PATENT SPECIFICATION (11) 1 583 163

1 583 163

(21) Application No. 18427/77 (22) Filed 3 May 1977
(31) Convention Application No. 2619638
(32) Filed 4 May 1976 in
(33) Federal Republic of Germany (DE)
(44) Complete Specification published 21 Jan. 1981
(51) INT CL³ C07D 207/27
(52) Index at acceptance
C2C 1175 1177 1341 1510 1672 200 202 215 220 225 226 22Y 246 247 248 250 251 253 254 259 25Y 28X 298 304 30Y 311 313 31Y 338 350 351 352 355 35Y 360 362 363 364 366 367 368 36Y 373 37Y 386 387 388 389 409 40Y 43X 463 464 46X 491 509 50Y 612 623 624 625 628 634 635 652 655 658 65X 662 672 694 695 697 761 762 771 802 80Y AA QU TA TT

(19)

(54) PYRROLIDONES AND PROCESS FOR THEIR MANUFACTURE

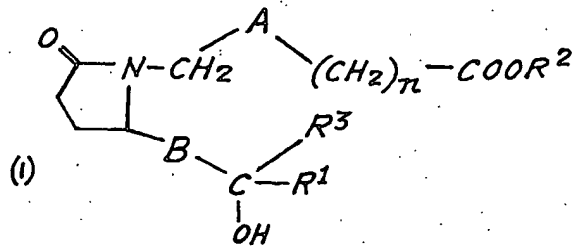
(71) We, HOECHST AKTIENGESELLSCHAFT, a body corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt (Main) 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pyrrolidones and to a process for their production.

Prostaglandins are a group of natural substances isolated from various animal tissues. In mammals they are responsible for numerous physiological effects. Natural prostaglandins have a carbon structure of, in general, 20 carbon atoms and are distinguished from one another, above all, by an increase or decrease in the number of hydroxyl groups or double bonds in the cyclopentane ring (with regard to the structure and effect of prostaglandins see *inter alia*, M. F. Cuthbert "The Prostaglandins, Pharmacological and Therapeutic Advances", William Heinemann Medical Books Ltd., London, (1973)).

The synthesis of analogues of prostanoic acids that do not occur naturally and in which the plurality of the pharmacological effects of natural prostaglandins are differentiated is increasingly gaining in importance. In German Offenlegungsschriften 2 528 664 and 2 556 326 prostaglandins in which the carbon in the 8-position of the natural prostaglandins is replaced by nitrogen, are described for the first time. Independently of this, the synthesis of a single represenative of this type is described in Tetrahedron Letters 2931 (1975).

The present invention provides a compound of the general formula I



(I)

in which

R^1 represents a straight or branched chain, saturated or unsaturated aliphatic hydrocarbon radical having up to 10 carbon atoms or a cycloaliphatic hydrocarbon radical having 3—7 carbon atoms, which radicals can each be substituted by

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio radical having up to 5 carbon atoms,

b) a phenoxy radical which may itself be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from halogen atoms, alkyl groups having 1—3 carbon atoms, phenoxy radicals, and alkoxy radicals having 1—4 carbon atoms which alkyl and phenoxy groups may be substituted by one or more halogen atoms,

c) a furyloxy, thienyloxy or benzyloxy radical, each of which may be monosubstituted or disubstituted in the nucleus by one or two substituents selected, independently in the latter case, from halogen atoms, alkyl groups having 1—3 carbon atoms, which may be substituted by one or more halogen atoms, and alkoxy groups having 1—4 carbon atoms,

d) a trifluoromethyl group or a pentafluoroethyl group,

e) a cycloalkyl radical having 3—7 carbon atoms,

f) a phenyl, thienyl, or furyl radical each of which may be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from halogen atoms, alkyl groups having 1—3 carbon atoms which may be substituted by one or more halogen atoms, and alkoxy groups having 1—4 carbon atoms,

R^2 represents a straight or branched chain, saturated or unsaturated aliphatic or cycloaliphatic radical having 2—6 carbon atoms, an araliphatic hydrocarbyl radical having 7 or 8 carbon atoms or, if R^1, R^3, A, B and n do not simultaneously represent a hydrogen atom, an n-pentyl group, a $—CH_2—CH_2—$ group, a —CH=CH— group and the integer three respectively, a methyl group or a hydrogen atom,

R^3 represents a hydrogen atom or a straight or branched chain alkyl, alkenyl, or alkynyl radical having up to 5 carbon atoms or an araliphatic hydrocarbyl radical having 7 or 8 carbon atoms,

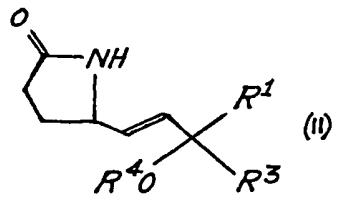
A and B each represents a $—CH_2—CH_2—$ or a —CH=CH— group, wherein A and B may be the same or different but may not simultaneously be a —CH=CH— group,

n represents the integer two, three or four.

The invention also provides the salts of the free acids of formula I, especially the physiologically tolerable salts thereof.

The present invention also provides a process for the production of a compound of the general formula I wherein

a_1) a compound of formula II

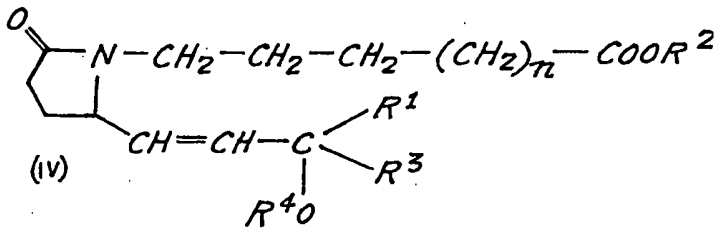


(II)

wherein R^1 and R^3 have the meanings given for formula I and R^4 represents a protective group that can be split off under acidic conditions, is deprotonated at the nitrogen atom with a base and the anion thus formed is reacted with a carboxylic acid derivative of formula III

$$Y—CH_2—CH_2—CH_2—(CH_2)_n—COOR^2 \qquad III$$

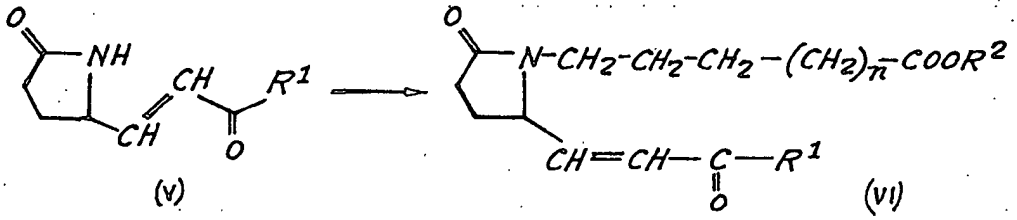
wherein R^2 and *n* have the meanings given for formula I and Y represents an alkanesulphonyloxy radical or a benzenesulphonyloxy radical that may be substituted by one or more substituents selected from alkyl groups and halogen atoms, or Y represents a halogen atom to form a compound of formula IV



(IV)

a_2) the hydroxy protective group R^4 is split off from the compound of formula IV by acid hydrolysis to form a compound of formula I in which A represents a $—CH_2—CH_2—$ group and B a —CH=CH— group, or

$a_{2.1}$) a compound of formula V is reacted as described under a_1) to form a compound of formula VI



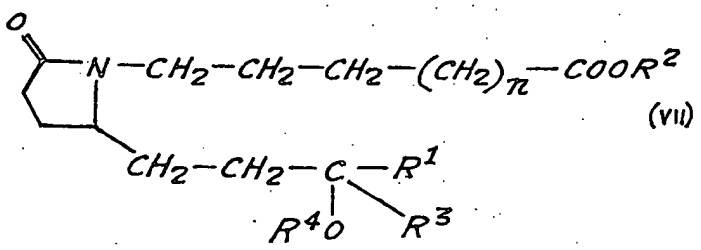
(V) (VI)

wherein R^1, R^2 and n have the meanings given for formula I,

$a_{2.2}$) the exocyclic carbonyl group in the compound of formula VI is reduced or the compound of formula VI is reacted with an organometallic compound, produced from R^3—X~, wherein X~ represents a halogen atom and R^3 has the meanings given for formula I with the exception of a hydrogen atom, to form a compound of formula I wherein A represents a $—CH_2—CH_2—$ group and B represents a —CH=CH— group, and optionally

a_3) a compound of formula I in which A represents a $—CH_2—CH_2—$ group and B represents a —CH=CH— group, is hydrogenated to form a compound of formula I wherein A and B each represent a $—CH_2—CH_2—$ group, or

$a_{3.1}$) a compound of formula IV is hydrogenated to form a compound of formula VII

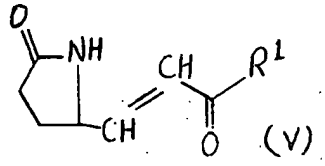


(VII)

wherein R^1, R^2, R^3 and n have the meanings given for formula I and R^4 is as defined above, and

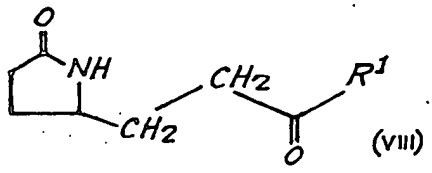
$a_{3.2}$) the hydroxy protective group R^4 in a compound of formula VII is split off by acid hydrolysis to give a compound of formula I wherein A and B each represents a $—CH_2—CH_2—$ group, or

$b_{1.1}$) in a compound of formula V



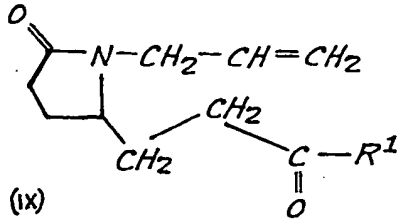
(V)

the double bond is hydrogenated to give a compound of formula VIII wherein R^1 has the meaning given for formula I



(VIII)

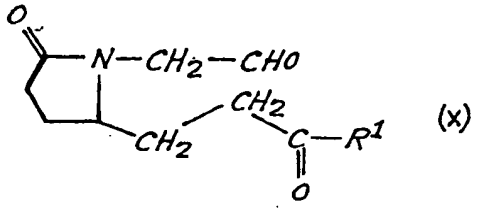
$b_{1.2}$) the compound of formula VIII is deprotonated at the nitrogen with a base and the anion formed is reacted with an allyl halide to form a compound of formula IX



(IX)

wherein R^1 has the meaning given for formula I,

$b_{1.3}$) the compound of formula IX obtained is subjected to ozonolysis whereby an aldehyde of formula X is formed



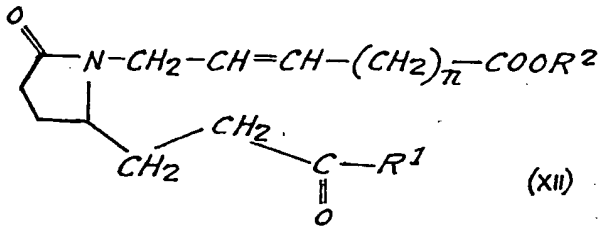
(X)

wherein R^1 has the meaning given for formula I,

$b_{1.4}$) the aldehyde of formula X obtained is reacted with an ylide of formula XI

$$(R^5)_3P=CH(CH_2)_nCOOR^2 \qquad XI$$

wherein n and R^2 have the meanings given for formula I and R^2 may also represent an alkali metal cation, the symbols R^5 each represents the same or different straight chain (C_1—C_4)-alkyl radical or phenyl radical, to form a compound of formula XII

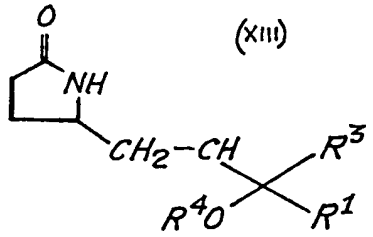


(XII)

wherein R^1, R^2 and n have the meanings given for formula I,

$b_{1.5}$) the exocyclic carbonyl group of the compound of formula XII is reacted with an organometallic compound produced from R^3—$X^{\sim}$, wherein $X^{\sim}$ represents a halogen atom and R^3 has the meaning given for formula I but may not be hydrogen, or the exocyclic carbonyl group of the compound of formula XII is reduced to form a compound of formula I wherein A represents a —CH=CH— group and B represents a —CH_2—CH_2— group, or

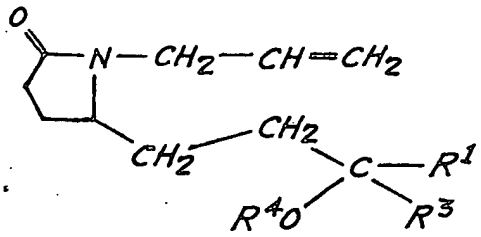
$b_{2.1}$) the double bond in a compound of formula II is hydrogenated to form a compound of formula XIII



(XIII)

wherein R^1 and R^3 have the meanings given for formula I and R^4 is as defined above,

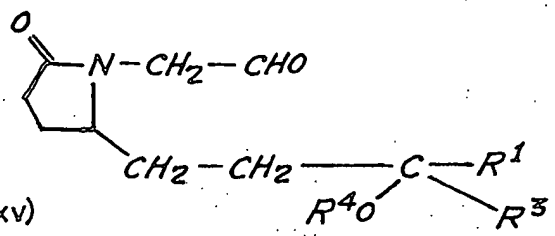
$b_{2.2}$) the compound of formula XIII is deprotonated at the nitrogen with a base and the anion formed is reacted with an allyl halide to form a compound of formula XIV



(XIV)

wherein R^1 and R^3 have the meanings given for formula I and R^4 is as defined above,

$b_{2.3}$) the compound of formula XIV is subjected to ozonolysis whereby an aldehyde of formula XV is formed



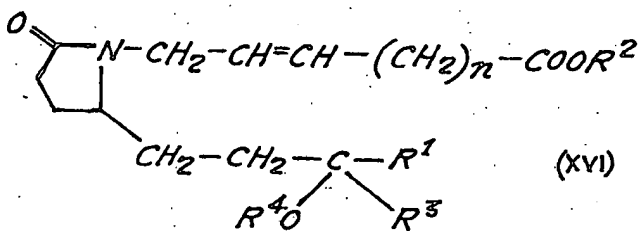
(XV)

wherein R^1 and R^3 have the meanings given for formula I and R^4 is as defined above,

$b_{2.4}$) the aldehyde of formula XV is reacted with an ylide of formula XI

$$(R^5)_3P=CH(CH_2)_nCOOR^2 \qquad XI$$

wherein n and R^2 have the meanings given for formula I and R^2 may also represent an alkali metal cation and the symbols R^5 is as defined above, to form a compound of formula XVI



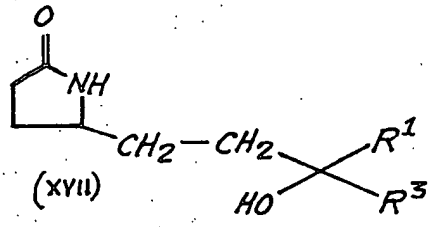
(XVI)

wherein R^1, R^2, R^3 and n have the meanings given for formula I and R^4 is as defined above,

$b_{2.5}$) the protective group R^4 is split off from the compound of formula XVI by acid hydrolysis to form a compound of formula I wherein A represents a —CH=CH— group and B represents a $—CH_2—CH_2—$ group, and optionally

b_3) a compound of formula I, wherein A represents a —CH=CH— group and B represents a $—CH_2—CH_2—$ group, is hydrogenated to form a compound of formula I wherein A and B each represent a $—CH_2—CH_2—$ group, or

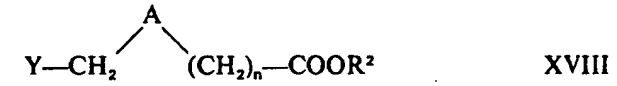
$b_{4.1}$) the exocyclic carbonyl group in the compound of formula VIII is reduced, or the compound of formula VIII is reacted with an organometallic compound produced from $R^3—X^{\sim}$, wherein $X^{\sim}$ represents a halogen atom and R^3 has the meaning mentioned for formula I but cannot represent hydrogen, to form a compound of formula XVII



(XVII)

wherein R^1 and R^3 hav the meanings given for formula I and

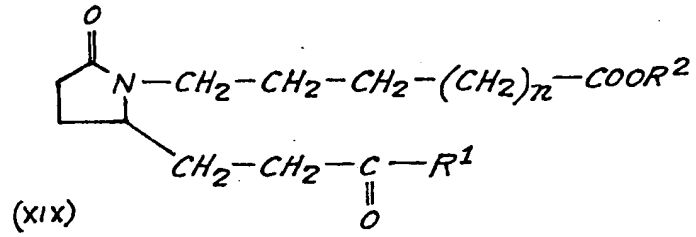
$b_{4.2}$) the compound of formula XVII is deprotonated at the nitrogen with a base and the anion formed is reacted with a carboxylic acid derivative of formula XVIII



XVIII

wherein R^2, A and n have the meanings given for formula I and Y is as defined above, whereby a compound of formula I is formed, wherein A represents a $-CH_2-CH_2-$ or a $-CH=CH-$ group and B represents a $-CH_2-CH_2-$ group, or

c_1) a compound of formula VIII is deprotonated at the nitrogen atom with a base and the anion formed is reacted with a carboxylic acid derivative of formula III whereby a compound of formula XIX is formed

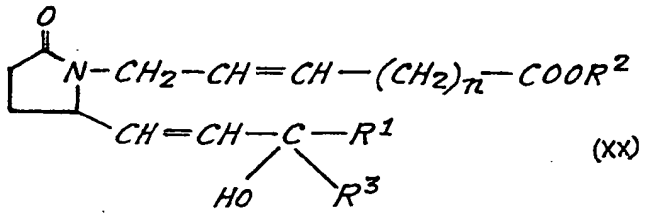


(XIX)

wherein R^1, R^2 and n have the meanings given for formula I and

c_2) the exocyclic carbonyl group of the compound of formula XIX is reduced, or the compound of formula XIX is reacted with an organometallic compound produced from $R^3-X^{\sim}$, wherein $X^{\sim}$ represents a halogen atom and R^3 has the meaning mentioned for formula I but cannot represent hydrogen, to form a compound of formula I wherein A and B each represent a $-CH_2-CH_2-$ group, or

d) a compound of formula XX



(XX)

is hydrogenated to form a compound of formula I wherein A and B each represent a $-CH_2-CH_2-$ group, or

e) any one or more of the steps defined above is carried out analogously using a reactant analogous to a compound as defined above but in which a free hydroxyl group is present instead of a group OR^4, or a group OR^4 is present instead of a free hydroxyl group, as appropriate, R^4 being as defined above, and

f) if desired, a free acid of formula I resulting from any of the above reactions is converted into a salt thereof, especially a physiologically tolerable salt.

Of the meanings given for the symbols R^1, R^2 and R^3, n, A and B, the following are preferred:

For R^1: a straight or branched chain, saturated or unsaturated, aliphatic radical having up to 7 carbon atoms or a cycloaliphatic radical having 5—7 carbon atoms, which radicals can each be substituted by

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio radical having up to 4 carbon atoms

b) a phenoxy radical which may itself be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from alkyl groups having 1—3 carbon atoms, methoxy and ethoxy groups, trifluoromethyl groups, halogen atoms, and phenoxy radicals which may be substituted by one or more halogen atoms,

c) a thienyloxy or benzyloxy radical, each of which may be monosubstituted or disubstituted by one or two substituents selected, independently in the

latter case, from alkyl groups having 1—3 carbon atoms, trifluoromethyl groups, halogen atoms, methoxy and ethoxy groups

d) a trifluoromethyl group,

e) a cycloalkyl radical having 5—7 carbon atoms,

f) a phenyl radical or thienyl radical each of which may be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from alkyl groups having 1—3 carbon atoms, trifluoromethyl groups, halogen atoms, and methoxy and ethoxy groups.

For R^2: a straight or branched chain alkyl radical having 1—6 carbon atoms, a straight or branched chain alkenyl radical having 2—4 carbon atoms, a cycloalkyl radical having 5 or 6 carbon atoms or an aralkyl radical having 7 or 8 carbon atoms.

For R^3: a hydrogen atom, a straight or branched chain alkyl radical having 1 to 5 carbon atoms, an alkenyl radical or alkynyl radical having 2 to 5 carbon atoms.

The following meanings, in particular, are preferred:

For R^1: a straight or branched chain alkyl radical having 1—7 carbon atoms, a straight or branched chain alkenyl radical having 3—5 carbon atoms or a cycloalkyl radical having 5—7 carbon atoms, which radicals may be substituted by:

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio radical having up to 3 carbon atoms,

b) a phenoxy radical which may itself be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms, and phenoxy radicals optionally substituted by chlorine and/or fluorine atoms,

c) a thienyloxy or benzyloxy radical each of which may be monosubstituted or disubstituted in the nucleus by one or two substituents selected independently in the latter case, from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms,

d) a trifluoromethyl group,

e) a cycloalkyl radical having 5—7 carbon atoms,

f) a phenyl radical or thienyl radical each of which may be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms,

For R^2: a straight chain alkyl radical having 1 to 6 carbon atoms, a branched chain alkyl radical having 3—5 carbon atoms, a straight chain alkenyl radical having 2—4 carbon atoms, a cyclopentyl or cyclohexyl radical or a benzyl radical.

For R^3: a hydrogen atom, a methyl, ethyl or propyl radical or an alkenyl or alkynyl radical having 2 or 3 carbon atoms, and *n* preferably represents the integer 3. Compounds in which B represents the $-CH_2-CH_2$ group are especially preferred.

Of the substituents for R^1 the following, for example, are particularly preferred:

2,2 - dimethylhexyl, 3,3 - dimethylhexyl, 4,4 - dimethylhexyl, 3 - ethylpentyl, 1,1 - dimethyl - 4 - pentenyl, 5 - methyl - 4 - hexenyl, 1 - methyl - 5 - cyclohexylpentyl, 4 - cycloheptylbutyl, 5,5,5 - trifluoropentyl, 6,6,6 - trifluorooctyl, 1,1 - dimethyl - 7,7,7 - trifluoroheptyl, 1 - methyl - 6,6,6 - trifluorohexyl, 1,1 - difluoro - 4,4 - dimethylpentyl, 4,4 - difluorocyclohexyl, 4 - trifluoromethylcyclohexyl, 3 - trifluoromethylcyclohexyl, 2 - trifluoromethylcycloheptyl, 3 - trifluoromethylcyclopentyl, 3,3 - dimethyl - 2 - oxapentyl, 3 - methyl - 2 - oxahexyl, 4,4 - dimethyl - 2 - oxapentyl, 1,1,4 - trimethyl - 2 - oxa - pentyl, 3,4 - dimethyl - 2 - oxapentyl, 5 - methyl - 2 - oxa - 4 - hexenyl, 2,2 - dimethyl - 3 - oxaheptyl, 1,1 - dimethyl - 3 - oxahexyl, 1,1 - dimethyl - 3 - oxaoctyl, 1,1,5,5 - tetramethyl - 3 - oxahexyl, 1 - methyl - 3 - oxahexyl, 1 - methyl - 3 - oxaoctyl, 1,1,6 - trimethyl - 3 - oxa - 5 - heptenyl, 1,1,6 - trimethyl - 3 - oxaheptyl, 7 - methyl - 4 - oxaoctyl, 1,1 - dimethyl - 4 - oxa - 6 - heptenyl, 4 - methoxycyclohexyl, 3 - butoxycyclohexyl, 2 - ethoxycyclohexyl, 3 - ethoxycyclopentyl, 4 - methoxycycloheptyl, 2 - thiapentyl, 2 - thiahexyl, 2 - thiaheptyl, 4,4 - dimethyl - 2 - thiapentyl, 5 - methyl - 2 - thia - 4 - hexenyl, 3 - thiapentyl, 3 - thiahexyl, 5,5 - dimethyl - 3 - thiahexyl, 1,1 - dimethyl - 3 - thiapentyl, 1,1 - dimethyl - 4 - thiapentyl, 4 - chlorophenoxymethyl, 2 - chlorophenoxymethyl, 2,3 - dichlorophenoxymethyl, 2,4 - dichlorophenoxymethyl, 2,5 - dichlorophenoxymethyl, 2,6 - dichlorophenoxymethyl, 3,4 - dichlorophenoxymethyl, 3,5 - dichlorophenoxymethyl, 2 - chloro - 6 - methylphenoxymethyl, 2 - chloro - 4 -

methylphenoxymethyl, 3 - chloro - 2 - methylphenoxymethyl, 4 - chloro - 2 - methylphenoxymethyl, 5 - chloro - 2 - methylphenoxymethyl, 4 - trifluoromethylphenoxymethyl, 2 - trifluoromethylphenoxymethyl, 2 - methyl - 5 - trifluoromethylphenoxymethyl, 3 - methyl - 5 - trifluoromethylphenoxymethyl, 3 - fluorophenoxymethyl, 2 - fluorophenoxymethyl, 2 - fluoro - 4 - trifluoromethylphenoxymethyl, 3,4 - difluorophenoxymethyl, 4 - fluoro - 2 - methylphenoxymethyl, 4 - phenoxyphenoxymethyl, 3 - *p* - chlorophenoxyphenoxymethyl, 4 - methoxyphenoxymethyl, 3 - methoxyphenoxymethyl, 4 - chloro - 3 - methoxyphenoxymethyl, 3 - chloro - 4 - methoxyphenoxymethyl, 4 - methoxy - 3 - methylphenoxymethyl, 4 - methoxy - 2 - methylphenoxymethyl, 3 - methoxy - 5 - methylphenoxymethyl, 2 - (3 - chlorophenoxy)ethyl, 2 - (4 - chlorophenoxy)ethyl, 2 - (3 - trifluoromethylphenoxy)ethyl, 2 - (4 - methoxyphenoxy)ethyl, 2 - (3 - methylphenoxy)ethyl, 2 - (4 - fluorophenoxy)ethyl, 2 - (3 - chloro - 5 - methylphenoxy)ethyl, 1 - methyl - 2 - (3 - trifluoromethylphenoxy)ethyl, 1 - methyl - 2 - (3 - chlorophenoxy)ethyl, 1 - methyl - 2 - (4 - fluorophenoxy)ethyl, 1 - methyl - 2 - (4 - chloro - 3 - methylphenoxy)ethyl, 1 - methyl - 2 - (3 - chloro - 4 - methoxyphenoxy)ethyl, 2 - (3 - trifluoromethyl - phenoxy) - 1,1 - dimethylethyl, 2 - (3 - chlorophenoxy) - 1,1 - dimethylethyl, 2 - (4 - fluorophenoxy) - 1,1 - dimethylethyl, 2 - (3,4 - dichlorophenoxy) - 1,1 - dimethylethyl, 2 - (3 - chloro - 4 - methylphenoxy) - 1,1 - dimethylethyl, 2 - (3 - chloro - 4 - phenoxyphenoxy) - 1,1 - dimethylethyl, 1,1 - dimethyl - 4 - phenoxybutyl, 1,1 - dimethyl - 4 - (3 - trifluoromethylphenoxy)butyl, benzyloxymethyl, 3 - chlorobenzyloxymethyl, 3 - trifluoromethylbenzyloxymethyl, 4 - methoxybenzyloxymethyl, 3 - phenoxybenzyloxymethyl, 2 - methylbenzyloxymethyl, 4 - chloro - 3 - methoxybenzyloxymethyl, 3 - methoxy - 5 - methylbenzyloxymethyl, 2 - (3 - chlorobenzyloxy) - 1,1 - dimethylethyl, 1 - methyl - 2 - (4 - trifluoromethylbenzyloxy)ethyl, 3 - (4 - fluorobenzyloxy)propyl, 4 - (3 - chlorophenoxy) - cyclohexyl, 4 - (3 - trifluoromethylphenoxy)cyclohexyl, 2 - phenoxycyclohexyl, 4 - (2 - chlorobenzyloxy) - cyclohexyl, benzyl, 3 - trifluoromethylbenzyl, 4 - methylbenzyl, 2 - (3 - chlorophenyl)ethyl, 2 - (4 - fluorophenyl)ethyl, α,α - dimethylphenethyl, 1,1 - dimethyl - 3 - phenylpropyl, 2 - methyl - 3 - thienyloxymethyl, 2 - chloro - 3 - thienyloxymethyl, 2 - chloro - 4 - thienyloxymethyl, 3 - chloro - 4 - thienyloxymethyl, 2,5 - dimethyl - 3 - thienyloxymethyl, 2 - chloro - 3 - methyl - 4 - thienyloxymethyl, 2 - thienyloxymethyl, 4 - methyl - 2 - thienyloxymethyl, 5 - chloro - 2 - thienyloxymethyl, 5 - chloro - 3 - methyl - 2 - thienyloxymethyl, 3,5 - dimethyl - 2 - thienyloxymethyl, 2 - (3 - thienyl) - 1,1 - dimethylethyl, 3 - (3 - thienyl) - 1 - methylpropyl, 3 - (2 - methoxy - 4 - thienyl) - propyl, 3 - thenyl, 2 - chloro - 4 - thenyl, 2 - methyl - 5 - thenyl, 4 - (3 - thienyl)butyl, 1,1 - dimethyl - 3 - (3 - thienyl)propyl, 2 - (4 - methoxy - 2 - thienyl)ethyl.

The compounds of formulae II (R^3=H) and V used as starting materials for the processes mentioned under a) may be synthesized according to the conditions mentioned in German Offenlegungsschrift 2 528 664. The compounds of formula II ($R^3 \neq H$) can be produced according to the information given in German Offenlegungsschrift 2 556 326.

The compounds of formulae II and V may be alkylated with a carboxylic acid derivative of formula II according to conventional methods, for example, the nitrogen is deprotonated with a suitable base, for example, sodium hydroxide or potassium hydroxide, sodium amide or potassium amide, sodium hydride, potassium tert.-butoxide lithium diisopropylamide or lithium cyclohexyl-isopropylamide, and then the alkylating agent of formula III is added as such or dissolved in a suitable appropriate solvent.

The radical Y in the compound of formula III is, for example, methanesulphonyloxy, *p* - bromobenzenesulphonyloxy, or *p* - toluenesulphonyloxy but chlorine, bromine and iodine atoms are preferred, bromine and iodine being of the most importance.

The reaction of the base with the compound of formulae II and V is effected with the exclusion of air and moisture because of the sensitivity to air and moisture of the bases and the resulting carbanions. Suitable solvents are, in particular, aprotic polar liquids which still have sufficient dissolving power even at low temperatures and which are inert under the reaction conditions. Optionally, a mixture of two or more solvents may be used to lower the solidification point.

Preferred solvents are, for example, ethers, for example, dimethyl ether, diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, and glycol dimethyl ether, also dimethylformamide, dimethyl sulphoxide, and toluene. The reaction temperatures are generally from −30°C to +100°C, preferably from −10°C to +80°C.

Working-up can, for example, be carried out by adding a predetermined amount of water to the reaction mixture, separating the organic phase, extracting the aqueous phase several times with an organic solvent and drying and concentrating the combined organic phases. In a very small number of cases the residue must be purified by high vacuum distillation but in most cases it can be purified by column chromatography. The products are often already so pure when formed that purification is not necessary.

A compound of formula I in which A is $-CH_2-CH_2-$, B is $-CH=CH-$ and R^3 is hydrogen can be obtained by treating the compound of formula VI with a reducing agent. Reduction can be effected with any reducing agent that renders possible the selective reduction of an exocyclic carbonyl group to form a hydroxyl group. Preferred reducing agents are complex metal hydrides, in particular borohydrides, for example, sodium borohydride, zinc borohydride or lithium perhydro-9b-boraphenalkyl hydride (J. Amer. Chem. Soc. *92*, 709 (1970)), and also complex aluminium hydrides, for example, sodium - bis - (2 - methoxyethoxy) - aluminium hydride. Reduction is normally carried out at a temperature of from −10° to +50°C in a solvent which is inert with regard to the hydrides, for example, an ether, for example, diethyl ether, 1,2 - dimethoxyethane, dioxane, tetrahydrofuran or diethylene glycol dimethyl ether or a hydrocarbon, for example, benzene, or in an alcohol/water mixture, for example, methanol/water. The isomeric α- and β-hydroxy compounds formed during this reduction can be separated into the two isomers by means of conventional chromatographic methods.

The organometallic compounds used for converting a compound of formula VI into a compound of formula I in which A is $-CH_2-CH_2-$, B is $-CH=CH-$ and R^3 does not represent a hydrogen atom, are derived from metals of the 1st and 2nd main groups. Particularly suitable compounds are organo - lithium and organo - magnesium compounds (Grignard compounds) that are produced in any of the usual ways, e.g., from a compound $R^3-X^{\sim}$, wherein R^3 has the meaning given for formula I and $X^{\sim}$ represents a halogen atom, for example, a chlorine, bromine or iodine atom, and the corresponding metal, for example Li or Mg.

Suitable solvents for the reaction of the pyrrolidones of formula VI are those that are inert under the reaction conditions, for example, hydrocarbons or, preferably, ethers, for example, diethyl ether, tetrahydrofuran and 1,2 - dimethoxyethane. The reaction is generally effected at a temperature of from −60°C to +30°C, preferably from −30°C to 0°C. The substrate may be added to the organometallic compound or the organometallic compound to the substrate, but the organometallic compound is preferably added to the substrate in order to prevent side reactions that might possibly occur. For working-up, water, a dilute mineral acid or a solution of an ammonium salt, for example, ammonium chloride in water, is added and the reaction product is isolated in the normal manner.

To split off the hydroxy protecting group from a compound of formula IV to give a compound of formula I (A: $-CH_2-CH_2-$, B: $-CH=CH-$), the usual reagents and reaction conditions may be used.

In the compound of formula IV, the hydroxy group is preferably protected by formation of an acetal group. The easiest method of splitting off this protective group, which results in a compound I, is by acidic hydrolysis with dilute aqueous/alcoholic acid, preferably in dilute aqueous/alcoholic oxalic acid at 10°—50°C or by heating with 50—70% acetic acid to 50—60°C.

The hydrogenation of a compound of formula I in which A is $-CH_2-CH_2-$ and B is $-CH=CH-$ to form the corresponding compound of formula I in which both A and B are $-CH_2-CH_2-$ may be carried out successfully under the conditions usual for hydrogenating a carbon-carbon double bond. Suitable catalysts are metal catalysts, for example, nickel, noble metal catalysts, for example, palladium as such or on a carrier, for example barium carbonate or an active carbon. An alcohol, for example, methanol, is generally used as a solvent. The temperature range and pressur range can vary to a great extent, the temperature range of from room temperature to 60°C and the pressure range of up to 10 atm being particularly important.

As described above, a compound of formula IV can alternatively be hydrogenated to form a compound of formula VII. Splitting off the hydroxy

protecting group from a compound of formula VII according to the instructions given for the conversion of IV to I (A: $-CH_2-CH_2-$, B: $-CH=CH-$) yields the corresponding compound of formula I (A,B: $-CH_2-CH_2-$).

The compounds of formula VI and I wherein R^3 represents hydrogen, can also be synthesized in a manner analogous to the instructions given in Tetrahedron Letters 2931 (1975).

The hydrogenation operations, i.e. the conversion of IV to VII, V into VIII, I (A: $-CH=CH-$, B: $-CH_2-CH_2-$, or A: $-CH_2-CH_2-$, B: $-CH=CH-$) into I (A,B: $-CH_2-CH_2-$), II into XIII, XX into I; alkylation operations, i.e. the conversion of VIII into IX, XVII into I, XIII into XIV, VIII into XIX; the introduction of the radial R^3, i.e. the conversion of XII into I (A: $-CH=CH-$, B: $-CH_2-CH_2-$), XIX into I (A,B: $-CH_2-CH_2-$) and the splitting off of the hydroxy protecting group R^4 (XVI into I), all steps in the process variants b), c) and d), may be effected under the conditions already described for process a), wherein, of the conditions mentioned, there is preferred for the introduction of the allyl radical into VIII or XIII, for the conversion into IX or XIV, the use of potassium hydroxide as the base in dimethyl sulphoxide at a temperature within the range of from +10°C to 40°C.

The conversion of an olefin of formula IX into an aldehyde of formula X by ozonolysis may be effected analogously to instructions given in literature (Chem. Rev. *58*, 990 (1958), Tetrah. Lett. *36*, 4273 (1966)) in the following manner:

The olefin is dissolved, optionally with the exclusion of moisture, in a predetermined amount of methanol with which a further halogenohydrocarbon, for example, methylene chloride, is optionally mixed. The equivalent amount of ozone is fed into this solution at temperatures within the range of from −100°C to −50°C, preferably at −70°C. A slight excess of ozone has no effect on the yield. Any excess ozone is then removed by an inert gas, dimethyl sulphide is added to reduce the products of ozonolysis and the mixture is then stirred for one hour at −10°C, one hour at 0°C and one hour at 20°C.

To isolate the resulting aldehyde, the solution is concentrated *in vacuo* at temperatures as low as possible, the residue is optionally treated with a saturated sodium bicarbonate solution and the product is subsequently extracted with a suitable solvent, preferably benzene, or the crude product is chromatographed directly.

The aldehyde may be used either directly for the following Wittig reaction or after purification, e.g., by column chromatography.

The compound of formula XII is obtained by reacting a phosphonium ylide of formula XI, in which R^5 preferably represents a phenyl radical and R^2 is preferably hydrogen, which has been replaced by a metal atom during the production of the ylide, with the aldehyde of formula X in a suitable solvent. The phosphonium ylides and the phosphonium salts on which they are based may be produced according to methods analogous to those described in literature, (J. Amer. Chem. Soc. *91*, 5675 (1969)).

Inorganic bases, for example, sodium hydride, sodium amide or lithium amide, or an organic base, for example, an alkali metal organometallic compound, for example, potassium *tert.*-butyloxide, butyllithium, lithium diisopropylamide or the sodium salt of dimethyl sulphoxide, may be used for the production of the ylide.

Suitable solvents are, for example, ethers, for example, diethyl ether, tetrahydrofuran, and diethylene glycol dimethyl ether, di-lower alkyl sulphoxide, for example, dimethyl sulphoxide, and amides of carboxylic acids, for example, dimethylformamide and N,N - dimethylacetamide, and hexamethylphosphoric acid triamide.

The preferred solvent is dimethyl sulphoxide. In particular, the sodium salt of dimethyl sulphoxide is used as the base. Under these conditions *cis*-double bonds are preferentially formed.

The production of the ylide and the subsequent reaction with the aldehyde may be carried out in one reaction vessel. The details of the procedure are, for example, as follows:

The solution of the phosphonium salt is added at room temperature with the exclusion of moisture and under inert gas to an equivalent of a base that is likewise dissolved in an aprotic solvent, generally dimethyl sulphoxide. After stirring for approximately 1 hour, a solution of 0.30 to 0.95 equivalents of the aldehyde are added. The reaction is complete after 2—24 hours. Acidification is effected with a mineral acid at −5°C to +5°C (provided R^2=H), the acid is extracted from the

reaction mixture with a suitable solvent, for example, diethyl ether, methylene chloride or benzene, the organic phase is dried and concentrated.

The reaction steps just described for converting IX into XII can also be applied, in a similar manner, to the conversion of XIV to XVI.

In addition to the processes described in detail here the invention also includes those processes that are derived in analogous manner from the reaction stages indicated here. Included in these processes are, in particular, those process steps that are effected on compounds that differ from one another only in an increased content or decreased content of one or various protective groups (e.g. conversion of XIII (R^4=H) into XVI (R^4=H).

The reduction of the exocyclic carbonyl group, which is introduced by the Horner reaction, or the reaction of this carbonyl group with an organo-metallic reagent yields a mixture of α- and β-isomers with regard to the resulting secondary or tertiary hydroxyl group. The separation into the two epimers can be effected either on these reaction products or, after any of the subsequent reaction stages. This means that all subsequent reactions, e.g. hydrogenation, conversion into the free acid or esterification or conversion into metal salts or amine salts can be effected either on the pure α- and β-isomers or on a mixture of α- and β-isomers.

If the various intermediates are not obtained in pure form, purification, e.g. by column, thin layer or high-pressure liquid chromatography is recommended.

The compounds of formula I have two asymmetric centres, *viz.* the carbon atom that carries the secondary or tertiary hydroxyl group, and the carbon atom adjacent to the nitrogen in the five-membered ring, which carbon atom corresponds to the 5-position in the pyrrolidone ring.

Since none of the reactions indicated yields sterically uniform products, the invention relates to all compounds of formula I irrespective of the steric arrangement at the various carbon atoms. As well as the two optically isomeric carbon atoms already mentioned above, this also applies to the geometrically isomeric compounds regarding the double bond. However, it can generally be assumed that, in the case of the Horner reaction, as a result of the reaction carried out, a *trans* linkage will mainly be obtained and the *cis*-product, occurring only to a slight extent, may be removed by chromatographic purification operations. Similarly, in the Wittig reaction for introducing the carboxyl side chain, the corresponding *cis*-olefin is chiefly formed. In this case, the *trans*-olefin occurring as a by-product may be separated by appropriate purification operations.

The geometry of the double bond predetermined in the carboxylic acid derivatives XVIII (A: —CH=CH—) is transferred by the alkylating operation to the subsequent end products. This means that, when using a *trans*-derivative XVIII (A: —CH=CH—), the product carries a *trans*-double bond in the carboxyl side chain. Analogously the same applies to the use of the *cis*-derivative XVIII (A: —CH=CH—).

On the basis of the possibilities for introducing the two double bonds, it may be assumed that the geometry of the double bond is uniform. The mixture of two diasteromers present as a result of the two optically isomeric carbon atoms can be separated, in the case of crystallizable derivatives, by fractional crystallisation or by means of chromatographic methods, for example, column gas, thin layer, or medium or high pressure liquid chromatography, into the two racemic diasteromers. The racemates may be split up into the optically active compounds according to conventional processes, for example, treatment of the compound of formula I (R^2=H) with an optically active base, for example, e.g. brucine.

Apart from the compounds mentioned in the examples, the following compounds, in particular, can also be produced.

TABLE I

1 - (5 - Methoxycarbonylpentyl) - 5 - (3 - hydroxy - octyl) - 2 - pyrrolidone
1 - (5 - Methoxycarbonylpentyl) - 5 - (3 - hydroxy - 4,4 - dimethyl - 5 - ethoxypentyl) - 2 - pyrrolidone
1 - (5 - Methoxycarbonylpentyl) - 5 - (3 - hydroxy - 7,7,8,8,8 - pentafluorooctyl) - 2 - pyrrolidone
1 - (5 - Methoxycarbonylpentyl) - 5 - [3 - hydroxy - 4 - (3 - thienyloxy)butyl] - 2 - pyrrolidone
1 - (5 - Methoxycarbonylpentyl) - 5 - [3 - hydroxy - 5 - phenyl - pentyl] - 2 - pyrrolidone
1 - (5 - Methoxycarbonylpentyl) - 5 - (3 - hydroxy - 4,4 - dimethyloctyl) - 2 - pyrrolidone

1 - (5 - Methoxycarbonylpentyl) - 5 - [3 - hydroxy - 4 - (3 - trifluoromethylphenoxy) - butyl] - 2 - pyrrolidone
1 - (7 - *n* - Propoxycarbonylheptyl) - 5 - (3 - hydroxy - 3 - allyloctyl) - 2 - pyrrolidone
1 - (7 - *iso* - Amyloxycarbonylheptyl) - 5 - (3 - hydroxy - 3 - isopropyloctyl) - 2 - pyrrolidone
1 - (7 - Carboxyheptyl) - 5 - [3 - hydroxy - 4 - (4 - methoxyphenoxy) - butyl] - 2 - pyrrolidone
1 - (5 - *n* - Butoxycarbonylpentyl) - 5 - [3 - hydroxy - 4 - (3 - chloro - 4 - methylphenoxy) - butyl] - 2 - pyrrolidone
1 - (6 - Carboxyhexyl) - 5 - [3 - hydroxy - 4 - (5 - methyl - 3 - thienyloxy)butyl] - 2 - pyrrolidone
1 - (6 - Phenylethoxycarbonylhexyl) - 5 - [3 - hydroxy - 4 - (4,5 - dimethyl - 3 - thienyloxy) - butyl] - 2 - pyrrolidone
1 - [6 - *n* - Butoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - octyl] - 2 - pyrrolidone
1 - [6 - *n* - Hexyloxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 3 - benzyloctyl] - 2 - pyrrolidone
1 - [5 - Ethoxycarbonyl - (*Z*) - 2 - pentenyl] - 5 - [3 - hydroxyoctyl] - 2 - pyrrolidone
1 - [7 - Phenethoxycarbonyl - (*Z*) - 2 - heptenyl] - 5 - [3 - hydroxyoctyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 3 - ethynyl - octyl] - 2 - pyrrolidone
1 - [7 - Methoxycarbonyl - (*Z*) - 2 - heptenyl] - 5 - [3 - hyroxyundecyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - (E,E) - 4,6 - octadienyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 5 - cyclopentyl - pentyl] - 2 - pyrrolidone
1 - [6 - Carboxy - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 5 - phenyl - butyl] - 2 - pyrrolidone - 2
1 - [6 - Carboxy - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 7,7,8,8,8 - pentafluorooctyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 5 - ethoxypentyl] - 2 - pyrrolidone
1 - [6 - *n* - Hexyloxycarbonyl - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 6 - methylthiohexyl] - 2 - pyrrolidone
1 - [6 - Carboxy - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 5 - *iso*butyloxy - 4,4 - dimethylpentyl] - 2 - pyrrolidone
1 - [5 - Carboxy - (*Z*) - 2 - pentenyl] - 5 - [3 - hydroxy - 5 - allylthio - 4,4 - dimethylpentyl] - 2 - pyrrolidone
1 - [5 - Carboxy - (*Z*) - 2 - pentenyl] - 5 - [3 - hydroxy - 4 - (4 - methylphenoxy) - butyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - (3 - chlorophenoxy) - butyl] - 2 - pyrrolidone
1 - [5 - Methoxycarbonyl - (*Z*) - 2 - pentyl] - 5 - [3 - hydroxy - 4 - (4 methoxyphenoxy) - butyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - (4 - phenoxyphenoxy) - butyl] - 2 - pyrrolidone
1 - [6 - Ethoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxyphenoxy) - 4 - methylbutyl] - 2 - pyrrolidone
1 - [5 - Ethoxycarbonyl - (*Z*) - 2 - pentenyl] - 5 - [3 - hydroxy - 4 - (3 - chlorophenoxy) - butyl] - 2 - pyrrolidone
1 - [5 - *Iso*propoxycarbonyl - (*Z*) - 2 - pentenyl] - 5 - [3 - hydroxy - 4 - (2 - chloro - 4 - methylphenoxy) - butyl] - 2 - pyrrolidone
1 - [7 - Methoxycarbonyl - (*Z*) - 2 - heptenyl] - 5 - [3 - hydroxy - 4 - benzyloxybutyl] - 2 - pyrrolidone
1 - [7 - Ethoxycarbonyl - (*Z*) - 2 - heptenyl] - 5 - [3 - hydroxy - 4 - (5 - methyl - 3 - thienyloxy) - butyl] - 2 - pyrrolidone
1 - [7 - Ethoxycarbonyl - (*Z*) - 2 - heptenyl] - 5 - [3 - hydroxy - 4 - (4,5 - dimethyl - 3 - thienyloxy) - butyl] - 2 - pyrrolidone
1 - [5 - Ethoxycarbonyl - (*E*) - 2 - pentenyl] - 5 - [3 - hydroxy - 4 - (4 - fluorobenzyloxy) - butyl] - 2 - pyrrolidone

1 - [6 - Carboxy - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - (3 - trifluoromethylbenzyloxy) - butyl] - 2 - pyrrolidone
1 - [6 - *n* - Hexyloxycarbonyl - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - (4 - methoxybenzyloxy) - butyl] - 2 - pyrrolidone
1 - [6 - Carboxy - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - (2 - chloro - 4 - methylbenzyloxy) - butyl] - 2 - pyrrolidone
1 - [6 - Carboxy - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 8,8,8 - trifluoromethyloctyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 3 - ethyl - 5 - cyclopentylpentyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - cycloheptylbutyl] - 2 - pyrrolidone
1 - [6 - Ethoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenyl) - butyl] - 2 - pyrrolidone
1 - [6 - *n* - Butoxycarbonyl - (*Z*) - 2 - hexenyl] - 5 - [3 - hydroxy - 5 - (3,4 - dichlorophenyl) - pentyl] - 2 - pyrrolidone
1 - [6 - Carboxy - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 5 - (4 - tolyl) - pentyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonyl - (*E*) - 2 - hexenyl] - 5 - [3 - hydroxy - 4 - (5 - methyl - 3 - thienyl) - butyl] - 2 - pyrrolidone
1 - [6 - Carboxy - (*E*) - hexenyl] - 5 - [3 - hydroxy - 4,4 - dimethyl - 5 - (4 - methoxyphenyl) - pentyl] - 2 - pyrrolidone
1 - [6 - *n* - Butoxycarbonylhexyl] - 5 - [3 - hydroxy - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [6 - *n* - Hexyloxycarbonylhexyl] - 5 - [3 - hydroxy - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [5 - Ethoxycarbonylpentyl] - 5 - [3 - hydroxy - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [7 - Ethoxycarbonylheptyl] - 5 - [3 - hydroxy - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [6 - Phenethoxycarbonylhexyl] - 5 - [3 - hydroxy - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [6 - *Iso*amyloxycarbonylhexyl] - 5 - [3 - hydroxy - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [6 - *Iso*propyloxycarbonylhexyl] - 5 - [3 - hydroxy - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonylhexyl] - 5 - [3 - hydroxy - 3 - *iso*propyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [6 - Carboxyhexyl] - 5 - [3 - hydroxy - 3 - ethynyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [6 - Carboxyhexyl] - 5 - [3 - hydroxy - 3 - benzyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonylhexyl] - 5 - [3 - hydroxy - 5 - ethoxy - (*E*) - 1 - pentenyl] - 2 - pyrrolidone
1 - [6 - *n* - Hexyloxycarbonylhexyl] - 5 - [3 - hydroxy - 6 - methylthio - (*E*) - 1 - hexenyl] - 2 - pyrrolidone
1 - [6 - Carboxyhexyl] - 5 - [3 - hydroxy - 5 - *iso*butoxy - 4,4 - dimethyl - (*E*) - 1 - pentenyl] - 2 - pyrrolidone
1 - [6 - Carboxyhexyl] - 5 - [3 - hydroxy - 5 - allylthio - 4,4 - dimethyl - (*E*) - 1 - pentenyl] - 2 - pyrrolidone
1 - [6 - Carboxyhexyl] - 5 - [3 - hydroxy - 4 - (4 - methylphenoxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonylhexyl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [5 - Methoxycarbonylpentyl] - 5 - [3 - hydroxy - 4 - (4 - methoxyphenoxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - Methoxycarbonylhexyl] - 5 - [3 - hydroxy - 4 - (4 - phenoxyphenoxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - Ethoxycarbonylhexyl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxyphenoxy) - 4 - methyl - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - Ethoxycarbonylhexyl] - 5 - [3 - hydroxy - 4 - (3 - chlorophenoxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - *Iso*propoxycarbonylhexyl] - 5 - [3 - hydroxy - 4 - (2 - chloro - 4 - methylph noxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone

1 - [6 - Methoxycarbonylhexyl] - 5 - [3 - hydroxy - 4 - benzyloxy - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - Ethoxycarbonylhexyl] - 5 - [3 - hydroxy - 4 - (5 - methyl - 3 - thienyloxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - Ethoxycarbonylhexyl] - 5 - [3 - hydroxy - 4 - (4,5 - dimethyl - 3 - thienyloxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [5 - Ethoxycarbonylpentyl] - 5 - [3 - hydroxy - 4 - (4 - fluorobenzyloxy - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - Carboxyhexyl] - 5 - [3 - hydroxy - 3 - methyl - 4 - (3 - trifluoromethylbenzyloxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - *n* - Hexyloxyhexyl] - 5 - [3 - hydroxy - 4 - (4 - methoxybenzyloxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [6 - Carboxyhexyl] - 5 - [3 - hydroxy - 4 - (2 - chloro - 4 - methylbenzyloxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [7 - Carboxyheptyl] - 5 - [3 - hydroxy - 8,8,8 - trifluoro - (*E*) - 1 - heptenyl] - 2 - pyrrolidone
1 - [7 - Methoxycarbonylheptyl] - 5 - [3 - hydroxy - 5 - cyclopentyl - (*E*) - 1 - pentenyl] - 2 - pyrrolidone
1 - [7 - Methoxycarbonylheptyl] - 5 - [3 - hydroxy - 4 - cycloheptyl - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [7 - Ethoxycarbonylheptyl] - 5 - [3 - hydroxy - 4 - (4 - chlorophenyl) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [5 - *n* - Butoxycarbonylpentyl] - 5 - [3 - hydroxy - 5 - (3,4 - dichlorophenyl) - (*E*) - 1 - pentenyl] - 2 - pyrrolidone
1 - [5 - Carboxypentyl] - 5 - [3 - hydroxy - 5 - (4 - tolyl) - (*E*) - 1 - pentenyl] - 2 - pyrrolidone
1 - [5 - Methoxycarbonylpentyl] - 5 - [3 - hydroxy - 4 - (5 - methyl - 3 - thienyl) - (*E*) - 1 - butenyl] - 2 - pyrrolidone
1 - [5 - Carboxypentyl] - 5 - [3 - hydroxy - 4,4 - dimethyl - 5 - (4 - methoxyphenyl) - (*E*) - 1 - pentenyl] - 2 - pyrrolidone

The compounds of the invention have spasmogenic, bronchodilatory, vasoactive (i.e. vasoconstricting and vasodilating), and abortive properties and also properties regarding inhibition of the secretin of gastric juices. They may therefore be used as medicaments.

The invention accordingly provides a pharmaceutical preparation which comprises a compound of the general formula I or a physiologically tolerable salt thereof as active substance, in admixture or conjunction with a pharmaceutically suitable carrier.

Inorganic, physiologically tolerable salts are, for example, alkali metal salts, salts of the alkaline-earth metals and ammonium salts, and salts with organic bases are, for example, those derived from primary, secondary or tertiary amines, for example, salts with methyl, triethyl, benzyl, phenethyl, and allyl amines, and with piperidine, pyrrolidine, morpholine, ethanolamine, triethanolamine, and tris-(hydroxymethyl) methylamine. Esters of formula I are preferably the esters with lower aliphatic alcohols, for example, methyl, ethyl, propyl, butyl and hexyl esters, as well as the benzyl ester.

The active substance may be in the form of an aqueous solution or suspension, or may be dissolved or suspended in a pharmaceutically suitable organic solvent, for example, a monovalent or polyvalent alcohol, for example, ethanol, ethylene glycol or glycerin, an oil, for example, sunflower oil or cod liver oil, an ether, for example, diethylene glycol dimethyl ether, a polyether, for example, polyethylene glycol, or in the presence of a pharmaceutically suitable polymer carrier, for example, polyvinylpyrrolidine.

Preparations of the invention may be in a form suitable for infusion or injection, for oral administration, for example, tablets, or for local administration, for example, creams, emulsions, suppositories and, especially, aerosols.

The pharmaceutical preparations may also comprise one or more other active substances, for instance, compounds and hormones affecting fertility, for example, LH—RH (Luteinising hormone releasing hormone), FSH, oestradiol and LH, diuretic agents, for example, furosemide, anti-diabetic agents, for example, glycodiazine, tolbutamide, glibenclamid, phenformin, buformin, metformin, circulatory agents in the widest sense, e.g. coronary dilators for example, chromonar or prenylamine, hypotensors, for example, reserpine, α-methyldopa, clonidine anti-arrhythmic agents, lipid reducers and geriatric agents and other metabolically active

preparations, psychopharmacological agents, for example, chlordiazepoxide, diazepam and meprobamate, as well as vitamins, prostaglandins, compounds similar to prostaglandins and also prostaglandin antagonists.

The compounds of formulae IV, VI, VII, VIII, IX, X, XII, XIII, XIV, XV, XVI, XVII and XIX are valuable new intermediate products for the preparation of compounds of formula I, and the compounds of formulae IV, VI, VII, XII, XVI and XIX are themselves part of the invention.

The following examples illustrate the invention. The preparations of solvents used in chromatography are by volume.

Example 1

1. 1-(6-methoxycarbonylhexanyl)-5-(3-hydroxyoctyl)-2-pyrrolidone

1 mmol of 1 - (6 - methoxycarbonyl - (*Z*) - 2 - hexenyl) - 5 - (3 - hydroxy - (*E*) - 1 - octenyl) - 2 - pyrrolidone is dissolved in 10 ml of ethanol and hydrogenated with 5% palladium on carbon at normal pressure and room temperature. The catalyst is filtered off after the absorption of hydrogen is complete, the solvent is concentrated and the remaining oil is chromatographed. Chromatography: toluene/ethyl acetate/methanol 5:4:0.3

NMR	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
IR	1680 cm^{-1}	$\nu C=0$		
	1735 cm^{-1}	$\nu C=0$		

The following compounds are synthesized from the basic di-unsaturated compounds as indicated in the above instructions. Unless otherwise indicated, the chromatographic purification of the compounds was effected on silica gel with the eluting agent:

Toluene/ethyl acetate/methanol 5:4:0.3

2. 1-(6-methoxycarbonylhexyl)-5-(3-hydroxydecanyl)-2-pyrrolidone

NMR	δ=3.65 ppm	(s)	$COOCH_3$	3 protons
IR	1680 cm^{-1}	$\nu C=0$		
	1735 cm^{-1}	$\nu C=0$		

3. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 4,4,dimethyl - 5 - ethoxypentyl) - 2 - pyrrolidone

NMR	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
IR	1685 cm^{-1}	$\nu C=0$		
	1735 cm^{-1}	$\nu C=0$		

4. 1 - (6 - methoxycarbonylhexyl) - 5 - [3 - hydroxy - 4 - (4 - chlorophenoxy) - phenoxy - 4,4 - dimethylbutyl] - 2 - pyrrolidone

NMR	δ=1.05 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=3.7 ppm	(s)	$COOCH_3$	6 protons
	δ=6.9—7.9 ppm	(m) aromatic	protons	8 protons
IR	1680 cm^{-1}	$\nu C=0$		
	1730 cm^{-1}	$\nu C=0$		

5. 1 - (6 - methoxycarbonylhexyl) - 5 - [3 - hydroxy - 4 - (3 - thienyloxy) - butyl] - 2 - pyrrolidone

NMR	δ=3.7 ppm	(s)		3 protons
	δ=5.7 ppm	(m)	thiophene protons	3 protons
IR	1685 cm^{-1}	$\nu C=0$		
	1730 cm^{-1}	$\nu C=0$		

6. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 7,7,8,8,8 - pentafluorooctyl) - 2 - pyrrolidone

NMR	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
IR	1675 cm^{-1}	$\nu C=0$		
	1730 cm^{-1}	$\nu C=0$		

7. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 5 - cyclopentyl - 4,4 - dimethylpentyl) - 2 - pyrrolidone

NMR	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=3.65 ppm	(s)	$COOCH_3$	3 protons

8. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 5 - phenylpentyl) - 2 - pyrrolidone

NMR	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
	δ=7.3 ppm	(s)	C_6H_5	5 protons
IR	1682 cm^{-1}	νC=0		
	1730 cm^{-1}	νC=0		

9. 1 - (6 - methoxycarbonylhexyl) - 5 - [3 - hydroxy - 5 - (4 - methyl - 2 - chlorophenyl - 4,4 - dimethylpentyl] - 2 - pyrrolidone
Chromatography toluene/ethyl acetate 5:4

NMR	δ=1.0 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=2.25 ppm	(s)	CH_3	3 protons
	δ=7.1—7.5 ppm	(m)	aromatic protons	3 protons
IR	1670 cm^{-1}	νC=0		
	1735 cm^{-1}	νC=0		

10. 1 - (6 - ethoxycarbonylhexyl) - 5 - (3 - hydroxy - 7 - methyloctyl) - 2 - pyrrolidone

NMR	δ=1.0 ppm	(d)	$CH(CH_3)_2$	6 protons
	δ=1.25 ppm	(t)	$COOCH_2CH_3$	3 protons
IR	1685 cm^{-1}	νC=0		
	1725 cm^{-1}	νC=0		

11. 1 - (6 - ethoxycarbonylhexyl) - 5 - (3 - hydroxy - 4,4 - dimethyloctyl) - 2 - pyrrolidone

NMR	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons
IR	1680 cm^{-1}	νC=0		
	1735 cm^{-1}	νC=0		

12. 1 - (6 - ethoxycarbonylhexyl) - 5 - (3 - hydroxy - 4 - (3 - trifluoromethylphenoxy) - butyl) - 2 - pyrrolidone

NMR	δ=1.1 ppm	(t)	$COOCH_2CH_3$	3 protons
	δ=7.1—7.4 ppm	(m)	aromatic protons	4 protons
IR	1678 cm^{-1}	νC=0		
	1730 cm^{-1}	νC=0		

13. 1 - (6 - ethoxycarbonylhexyl) - 5 - [3 - hydroxy - 4 - (4 - chlorobenzyloxy) - butyl] - 2 - pyrrolidone

NMR	δ=1.1 ppm	(t)	$COOCH_2CH_3$	3 protons
	δ=7.0—7.5 ppm	(m)	aromatic protons	4 protons
IR	1680 cm^{-1}	νC=0		
	1735 cm^{-1}	νC=0		

14. 1 - (6 - ethoxycarbonylhexyl) - 5 - [3 - hydroxy - 4 - (2 - thienyl) - butyl] - 2 - pyrrolidone

NMR	δ=7.1—7.3 ppm	(m)	thiophene protons	3 protons
	δ=1.1 ppm	(t)	$COOCH_2CH_3$	3 protons
IR	1680 cm^{-1}	νC=0		
	1740 cm^{-1}	νC=0		

15. 1 - (7 - ethoxycarbonylheptyl) - 5 - (3 - hydroxy - 5 - ethoxy - 4,4 - dimethylpentyl) - 2 - pyrrolidone

NMR	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=1.2 ppm	(t)	$COOCH_2\underline{CH_3}$	3 protons
IR	1675 cm^{-1}	νC=0		
	1730 cm^{-1}	νC=0		

16. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 3 - methyloctyl) - 2 - pyrrolidone

NMR	δ=1.3 ppm	(s)	$C(CH_3)$	3 protons
	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
IR	1680 cm^{-1}	νC=0		
	1735 cm^{-1}	νC=0		

17. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 3,4,4 - trimethyl - 5 - ethoxypentenyl) - 2 - pyrrolidone

NMR	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=1.4 ppm	(s)	$—CH_3$	3 protons
	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
IR	1680 cm^{-1}	νC=0		
	1728 cm^{-1}	νC=0		

18. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 3 - benzyldecyl) - 2 - pyrrolidone

NMR	δ=7.1—7.3 ppm	(m)	C_6H_5	5 protons
	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
IR	1675 cm^{-1}	νC=0		
	1730 cm^{-1}	νC=0		

Example 2

a) (VIII)

5 - (3 - oxooctyl) - 2 - pyrrolidone

The 5 - (3 - oxo - (*E*) - 1 - octenyl) - 2 - pyrrolidone is hydrogenated to form 5 - (3 - oxooctyl) - 2 - pyrrolidone as described in Example 1 No. 1. The crude product is used for further reaction.

IR	1680 cm^{-1}	νC=0
	1705 cm^{-1}	νC=0 not completely resolved absorptions

b) (XIX)

1 - (6 - methoxycarbonylhexyl) - 5 - (3 - oxooctyl) - 2 - pyrrolidone

1 mmol of 5 - (3 - oxooctyl) - 2 - pyrrolidone is dissolved in 10 ml of dimethylformamide, 1 mmol of sodium hydride is added and the whole is stirred for 1 1/2 hours at 50°C. After adding catalytic amounts of sodium iodide, 1.2 mmol of 6 - bromohexanoic acid methyl ester is dissolved in 5 ml of dimethylformamide is added and the whole is then kept for a further 5 hours at this temperature. Water is added for working-up, the whole is shaken several times with ether, the organic phases are purified, dried and concentrated.

Chromatography: carbon tetrachloride/acetone 7:3

NMR	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
IR	1675 cm^{-1}	νC=0		
	1705 cm^{-1}	νC=0		
	1740 cm^{-1}	νC=0		

c) (I)

1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 3 - ethynyloctyl) - 2 - pyrrolidone

A solution of 10 mmol of 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - oxooctyl) - 2 - pyrrolidone in 70 ml of ether is cooled under nitrogen to −10°C. While stirring, 12 ml of a 1 molar solution of lithium acetylide in tetrahydrofuran is added and the whole is stirred for 30 minutes. ~1.5 ml of a saturated ammonium chloride solution are then added at 0°C. After approximately ten minutes, anhydrous magnesium chloride is added and suction filtering, concentration and chromatography are effected.

(*SiO*$_2$: toluene/ethyl acete/methanol 5:4:0.1)

NMR	δ=3.6 ppm	(s)	$COOCH_3$	3 protons	
	δ=2.7 ppm	(s)	C≡CH	1 proton	
IR	1735 cm^{-1}	νC=0			
	1685 cm^{-1}	νC=0			

Example 3

a) (VII)

1. 5 - (3 - oxodecyl) - 2 - pyrrolidone

By hydrogenation of 5 - (3 - oxo - (*E*) - 1 - decenyl) - 2 - pyrrolidone according to Example 2a.

IR	1705 cm^{-1}	νC=0
	1675 cm^{-1}	νC=0

2. 5 - (3 - oxo - 4,4 - dimethyloctyl) - 2 - pyrrolidone

By hydrogenation of 5 - (3 - oxo - (*E*) - 1 - octenyl) - 2 - pyrrolidone according to Example 2a.

NMR	δ=1.05 ppm	(s)	$C(CH_3)_2$	6 protons
IR	1700 cm^{-1}	νC=0		
	1670 cm^{-1}	νC=0		

3. 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxypentyl) - 2 - pyrrolidone

By hydrogenation of 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxy - (*E*) - 1 - pentenyl) - 2 - pyrrolidone in a manner analogous to that in Example 2a.

NMR	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons
IR	1680 cm^{-1}	νC=0		
	1710 cm^{-1}	νC=0		

4. 5 - [3 - oxo - 4 - (3 - trifluoromethylphenoxy) - butyl] - 2 - pyrrolidone

By hydrogenation of 5 - [3 - oxo - 4 - (3 - trifluoromethylphenoxy) - (*E*) - 1 - butenyl] - 2 - pyrrolidone in a manner analogous to that in Example 2a.

NMR	δ=4.5 ppm	(s)	CH_2	2 protons
IR	1680 cm^{-1}	νC=0		
	1700 cm^{-1}	νC=0		

The compounds synthesized under 1 to 4 are used as the crude products for further reactions.

b) (IX)

1. 1 - allyl - 5 - (3 - oxodecenyl) - pyrrolidone - 2

2.5 mmol of 5 - (3 - oxodecyl) - 2 - pyrrolidone are dissolved in 15 ml of dimethyl sulfoxide (dried) and 3 mmol of potassium hydroxide are added. While cooling with ice, 3 mmol of allyl bromide dissolved in 3 ml of dimethyl sulfoxide are added dropwise. The whole is then stirred for 2 hours in the course of which the reaction solution comes up to room temperature. Water is added and the product is extracted with ether, the organic phases are combined, dried, concentrated and chromatographed.

Chromatographic separation takes place, as in the following 4 Examples, on silica gel with toluene/ethyl acetate 5:4 as the eluting agent.

NMR	δ=5.0—6.2 ppm	(m)	$CH=CH_2$	3 protons
IR	1700 cm^{-1}	νC=0		
	1685 cm^{-1}	νC=0		

2. 1 - allyl - 5 - (3 - oxo - 4,4 - dimethyloctyl) - 2 - pyrrolidone
By alkylation of 5 - (3 - oxo - 4,4 - dimethyloctyl) - 2 - pyrrolidone with allyl bromide in a manner analogous to that in Example 3 b 1.

NMR	δ=5.0—6.2 ppm	(m)	$CH=CH_2$	3 protons
	δ=1.05 ppm	(s)	$C(CH_3)_2$	6 protons
IR	1705 cm^{-1}	$\nu C=0$		
	1675 cm^{-1}	$\nu C=0$		

3. 1 - allyl - 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxypentyl) - 2 - pyrrolidone
By alkylation of 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxy - pent - 1 - yl) - pyrrolidone - 2 with allyl bromide in a manner analogous to that in Example 3 b 1.

NMR	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=5.0—6.2 ppm	(m)	$CH=CH_2$	3 protons
IR	1680 cm^{-1}	$\nu C=0$		
	1705 cm^{-1}	$\nu C=0$		

4. 1 - allyl - 5 - [3 - oxo - 4 - (3 - trifluoromethylphenoxy) - butyl] - 2 pyrrolidone
By alkylation of 5 - [3 - oxo - 4 - (3 - trifluoromethylphenoxy) - butyl] - 2 - pyrrolidone with allyl bromide in a manner analogous to that in Example 3 b 1.

NMR	δ=4.5 ppm	(s)	CH_2	2 protons
	δ=5.0—6.2 ppm	(m)	$CH=CH_2$	3 protons
	δ=7.1—7.4 ppm	(m)	aromatic protons	4 protons
IR	1680 cm^{-1}	$\nu C=0$		
	1700 cm^{-1}	$\nu C=0$		

5. 1 - allyl - 5 - (3 - oxooctyl) - 2 - pyrrolidone
By alkylation of 5 - (3 - oxooctyl) - 2 - pyrrolidone with allyl bromide in a manner analogous to that in Example 3 b 1.

NMR	δ=5.0—6.2 ppm	(m)	$CH=CH_2$	3 protons
IR	1700 cm^{-1}	$\nu C=0$		
	1675 cm^{-1}	$\nu C=0$		

e) (X)

1. 1 - formylmethyl - 5 - (3 - oxodecyl) - 2 - pyrrolidone
0.02 mol of 1 - alkyl - 5 - (3 - oxodecyl) - 2 - pyrrolidone - 2 is dissolved in 100 ml of methylene chloride and 10 ml of methanol are added. The whole is cooled to −78°C and ozone is introduced at this temperature until the blue solution no longer becomes decolorized. The reaction mixture is heated to −20°C. At this temperature 0.2 mol of dimethyl sulfide are added dropwise. The cooling bath is removed and the reaction flask is left for two hours at room temperature.
The whole is concentrated and chromatographed.
(Silica gel: chloroform, acetone 8:2)

NMR	=9.6 ppm	CHO	1 proton

The following 1-formylmethyl compounds are prepared by ozonolysis from the 1-allyl compounds, as described above.

2. 1 - formylmethyl - 5 - (3 - oxo - 4,4 - dimethyloctyl) - 2 - pyrrolidone
chromatography chloroform/acetone 8:2

NMR	δ=9.6 ppm	CHO	1 proton

3. 1 - formylmethyl - 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxypentyl) - 2 - pyrrolidone
chromatography: carbon tetrachloride/acetone 7:3

NMR	δ=9.5 ppm	CHO	1 proton
	δ=0.9 ppm	$C(CH_3)_2$	6 protons

4. 1 - formylmethyl - 5 - [3 - oxo - 4 - (3 - trifluoromethylphenoxy) - butyl] - 2 - pyrrolidone
chromatography chloroform/acetone 8:2

NMR	δ=4.4 ppm	(s)	CH_2	2 protons
	δ=7.1—7.4 ppm	(m)	aromatic protons	4 protons
	δ=9.3 ppm		CHO	1 proton

5. 1 - formylmethyl - 5 - (3 - oxooctyl) - 2 - pyrrolidone
chromatography: chloroform/ethyl acetate 4:1

NMR	δ=9.6 ppm		CHO	1 proton

d) (XII)

1. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - oxodecyl) - 2 - pyrrolidone
0.01 mol of sodium hydride is stirred in 5 ml of dimethyl sulfoxide at 60°C until the evolution of hydrogen is complete. The whole is then cooled to room temperature and 5 mmol of 4 - carboxybutyl - triphenylphosphonium bromide dissolved in 5 ml of dimethyl sulfoxide are added. The whole is stirred for 30 minutes at room temperature. 2 mmol of 1 - formylmethyl - 5 - (3 - oxodecyl) - 2 - pyrrolidone dissolved in 3 ml of dimethyl sulfoxide are then added and the whole is subsequently heated to 50°C. Stirring is effected for three hours at this temperature. After cooling, 40 ml of water are added and the pH value is adjusted to 2 with a 5% strength solution of sodium hydrogen sulfate. Extraction with ether, drying and concentration are effected.
chromatography: chloroform/methanol 95:5

NMR	δ=5.2—5.7 ppm	(m)	CH=CH	2 protons

The following four 1 - (6 - carboxy - (Z) - 2 - hexenyl) compounds are prepared, as described above, from the corresponding 1 - formylmethyl compounds by Wittig reaction with (4 - carboxybutylidene) - triphenylphosphorane.

2. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - oxo - 4,4 - dimethyloctyl) - 2 - pyrrolidone
chromatography: toluene/ethyl acetate/glacial acetic acid 5:4:0.0

NMR	δ=5.3—5.5 ppm	(m)	CH=CH	2 protons
	δ=1.05 ppm	(s)	$C(CH_3)_2$	6 protons

3. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxy - pentyl) - 2 - pyrrolidone
chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.3—5.5 ppm	(m)	CH=CH	2 protons
	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons

4. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - [3 - oxo - 4(3 - trifluoromethylphenoxy) - butyl] - 2 - pyrrolidone
chromatography: chloroform/methanol 95.5

NMR	δ=5.1—5.2 ppm	(m)	CH=CH	2 protons
	δ=7.1—7.4 ppm	(m)	aromatic protons	4 protons
	δ=4.4 ppm	(s)	CH_2	2 protons

5. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - oxooctyl) - 2 - pyrrolidone
chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.2—5.5 ppm	(m)	CH=CH	2 protons

6. 1 - 5 - carboxy - (Z) - 2 - pentenyl) - 5 - (3 - oxooctyl) - 2 - pyrrolidone
From 1 - formylmethyl - 5 - (3 - oxooctyl) - 2 - pyrrolidone and (3 - carboxypropylidenetriphenylphosphorane according to Example 3 d 1.
chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.1—5.3 ppm	(m)	CH=CH	2 protons

7. 1 - (7 - carboxy - (Z) - 2 - heptenyl) - 5 - (3 - oxooctyl) - 2 - pyrrolidone
From 1 - formylmethyl - 5 - (3 - oxooctyl) - 2 - pyrrolidone - 2 and (5 - carboxypentylidene)triphenylphosphorane according to Example 3 d 1.
Chromatography: ethyl acetate/toluene/glacial acetic acid 4:5:0.01

NMR	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons

e) (I)

1. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - hydroxydecyl) - 2 - pyrrolidone
4 mmol of anhydrous zinc chloride are suspended in 10 ml of 1,2 - dimethoxyethane and 16 mmol of sodium borohydride are carefully added. The whole is then stirred for one hour at room temperature. Filtering off is effected and 0.8 mmol of 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - oxodecyl) - 2 - pyrrolidone dissolved in 2 ml of dimethoxyethane are added dropwise within 10 minutes to the solution thus obtained and the whole is then stirred for 2 1/2 hours at room temperature. Acidification with glacial acetic acid, concentration and chromatography are effected (silica gel: ethyl acetate/glacial acetic acid 98:2).

NMR	δ=5.3—5.5 ppm	(m)	CH=CH	2 protons
IR	1680 cm^{-1}	νC=0		
	1700 cm^{-1}	νC=0		
	~3200 cm^{-1}	broad absorption νO—H		

The following compounds indicated under 2 to 7 are produced from the basic ketones by reduction as described under 1). Chromatographic purification is, in these cases, effected exclusively on silica gel with ethyl acetate/glacial acetic acid 98:2.

2. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - hydroxy - 4,4 - dimethyloctyl) - 2 - pyrrolidone

NMR	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons
	δ=0.95 ppm	(s)	$C(CH_3)_2$	6 protons

3. 1 - (6 - carboxy - (Z) - 2 - hexen - 1 - yl) - 5 - (3 - hydroxy - 4,4 - dimethyl - 5 - ethoxypentyl) - 2 - pyrrolidone

NMR	δ=5.1—5.3 ppm	(m)	CH=CH	2 protons
	δ=0.9 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=1.1 ppm	(t)	OCH_2CH_3	3 protons

4. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - [3 - hydroxy - 4 - (3 - trifluoromethylphenoxy) - butyl] - 2 - pyrrolidone

NMR	δ=5.1—5.25 ppm	(m)	CH=CH	2 protons
	δ=4.4 ppm	(d)	CH_2	2 protons
	δ=7.2—7.4 ppm	(m)	aromatic protons	4 protons

5. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone

NMR	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons
IR	1680 cm^{-1} } 1700 cm^{-1} }	νC=0 absorptions not completely resolved.		

6. 1 - (5 - carboxy - (Z) - 2 - pentyl) - 5 - (3 - hydroxyoct - 1 - yl) - 2 - pyrrolidone

NMR	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons
	1680 cm^{-1}	νC=0		
	1700 cm^{-1}	νC=0		

7. 1 - (7 - carboxy - (Z) - 2 - heptenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone

NMR	δ=5.25—5.4 ppm	(m)	CH=CH	2 protons
IR	broad absorption at 1680—1700 cm^{-1} νC=0			

8. 1 - (6 - carboxy - (Z) - hexenyl) - 5 - (3 - hydroxy - 3 - methyloctyl) - 2 - pyrrolidone

From the compound of Example 3 b 5 by reaction with methyl-magnesium iodine in a manner analogous to that in Example 2 c.
Chromatography: toluene/ethyl acetate/glacial acetic acid 50:50:2

NMR	δ=2.3 ppm	(s)	CH_3	3 protons
	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons

9. 1 - (6 - carboxy - (Z) - hexenyl) - 5 - [3 - hydroxy - 3 - (allyloctyl] - 2 - pyrrolidone

From the compound of Example 3 b 5 by reaction with allylmagnesium bromide in a manner analogous to that in Example 2 c.
Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.0—6.2 ppm	(m)	CH=CH and $CH=CH_2$	5 protons
IR	1680 cm^{-1} and 1700 cm^{-1} the two absorption maxima not clearly resolved		(νC=0)	

10. 1 - (6 - methoxycarbonyl - (Z) - 2 - hexenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone

1 mmol of 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone is dissolved in 10 ml of 0.1 normal aqueous sodium hydroxide solution and the solvent is then concentrated. The remaining traces of water are removed under high vacuum. 8 ml of acetonitrile and 10 ml mol of methyl iodide are added and the whole is boiled for five hours under reflux. The reaction solution is distributed between water and ether, and the organic phase is dried, concentrated and chromatographed.
Eluting agent: toluene/ethyl acetate/methanol 5:4:0.3

NMR	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
	δ=5.2—5.35 ppm	(m)	CH=CH	2 protons
IR	1680 cm^{-1}	νC=0		
	1735 cm^{-1}	νC=0		

11. 1 - (6 - *n* - hexyloxycarbonyl - (Z) - 2 - hexenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone

Analogously to the above instructions from 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone and n - hexyl bromide.
Chromatography: toluene/ethyl acetate/methanol 5:4:0.1

NMR	δ=5.2—5.35 ppm	(m)	CH=CH	2 protons
	δ=4.2—4.4 ppm	(t) diffused signals	$COOCH_2$—	2 protons

f) (I)

1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone

By hydrogenation of 1 - (6 - methoxycarbonyl - (Z) - 2 - hexenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone analogously to Example 1. The physical data correspond to those of Example 1 No. 1.

g) (XVII)

5 - (3 - hydroxyoctyl) - 2 - pyrrolidone

By reduction of 5 - (3 - oxooctyl) - 2 - pyrrolidone with zinc borohydride analogously to Example 3 e 1.

Chromatography: chloroform/methanol 95:5

IR	1780 cm^{-1}	$\nu C=0$
MS	$M^{\oplus}$	=213

h) (I)

1. 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone

From 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone by alkylation with 6 - bromo - (*Z*) - 4 - hexene - 1 - carboxylic acid analogously to Example 3 b 1. The chromatographic conditions and physical-chemical data corresponding to Example 3 e 5.

2. 1 - (6 - carboxy - (E) - hexenyl) - 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone

From 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone by alkylation with 6 - bromo - (*E*) - 4 - hexene - 1 - carboxylic acid analogously to Example 3 b 1.

Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.1—5.35 ppm	CH=CH	2 protons
IR	1680 cm^{-1} and 1700 cm^{-1}	the two absorption maxima for $\nu C=0$ not completely resolved	

3. 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxyoct - 1 - yl) - 2 - pyrrolidone

From 5 - (3 - hydroxyoctyl) - 2 - pyrrolidone by alkylation with 6 - bromohexanecarboxylic acid analogously to Example 2 b.

Chromatography: ethyl acetate/glacial acetic acid 98:2

R_f-value: 0.25

i) (XIII)

5 - [3 - (tetrahydropyran - 2 - yl - oxy) - 3 - methyloctyl] - 2 - pyrrolidone

By hydrogenation of 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone according to the instructions given in Example 1, No. 1.

Chromatography: chloroform/ethyl acetate/methanol 5:4:0.5

NMR	δ=4.65 ppm	broad singlet	O—CH—O	1 proton
	δ=2.1 ppm	(s)	CH_3	3 protons
IR	1680 cm^{-1}	$\nu C=0$		

k) (XIV)

1 - allyl - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyloctyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyloctyl] - 2 - pyrrolidone by alkylation with allyl bromide analogously to Example 3 b 1.

Chromatography: carbon tetrachloride/acetone 7:3

NMR	δ=5.2—6.0 ppm	(m)	$CH=CH_2$	3 protons
	δ=4.65 ppm	broad singlet	O—CH—O	1 proton
	δ=2.05 ppm	(s)	CH_3	3 protons
IR	1680 cm^{-1}	$\nu C=0$		

l) (XV)

1 - formylmethyl - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyloctyl] - 2 - pyrrolidone

From 1 - allyl - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyloctyl] - 2 - pyrrolidone by ozonolysis analogous to Example 3 c 1.

Chromatography: toluene/ethyl acetate 5:4

NMR	δ=9.6 ppm	(s)	CHO	1 proton
	δ=4.6 ppm	broad singlet	O—CH—O	1 proton
	δ=2.05 ppm	(s)	CH_3	3 protons

m) (XVI)

1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyloctyl] - 2 - pyrrolidone

Analogous to Example 3 d l from 1 - formylmethyl - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyloctyl] - 2 - pyrrolidone and the 4 - carboxybutylidene)triphenylphosphorane.

Chromatography: toluene/ethyl acetate/glacial acetic acid 5:4:0.02

NMR	δ=5.2—5.5 ppm	(m)	CH=CH	2 protons
	δ=4.65 ppm	broad singlet	O—CH—O	1 proton

n) (I)

1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - (3 - hydroxy - 3 - methyloctyl) - 2 - pyrrolidone

0.05 mol of 1 - (6 - carboxy - (Z) - 2 - hexenyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyloctyl] - 2 - pyrrolidone is stirred in a mixture of 20 ml of ethanol and 10 ml of 6% strength aqueous oxalic acid for 4 hours at room temperature and then stirred for 4 hours at 40—45°C. The reaction mixture is then divided between ether and water and the aqueous phase is extracted several times with ether, the organic phase is dried and concentrated and the residue chromatographed.

For chromatographic conditions and physical-chemical properties see Example 3 e 8.

Example 4

a) (IV)

The compounds given under 1 to 9 are produced from the starting materials indicated in each case according to the instructions given in Example 2 b. When alkylating with an acid, the appopriate additional amount of sodium hydride must be used for neutralization of the acid.

1. 1 - (6 - carboxyhexyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - (E) - 1 - decenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - (*E*) - decenyl] - 2 - pyrrolidone and 6 - bromohexanecarboxylic acid.

Chromatography: ethyl acetate/toluene/methanol 4:5:0.2

NMR	δ=4.4 ppm broad singlet		O—CH—O	1 proton
	δ=5.1—5.4 ppm	(m)	CH=CH	2 protons

2. 1 - (6 - carboxyhexyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - (E) - 1 - octenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone and 6 - bromohexanecarboxylic acid.

Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=1.0 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons
	δ=4.5 ppm broad	singlet	O—CH—O	1 proton

3. 1 - (6 - carboxyhexyl) - 5 - [5 - (tetrahydropyran - 2 - yloxy) - 5 - phenyl - (E) - 1 - pentenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - 5 - phenyl - (*E*) - 1 - pentenyl] - 2 - pyrrolidone and 6 - bromohexanecarboxylic acid.

Chromatography: carbon tetrachloride/acetone 7:3

NMR	δ=4.4 ppm broad	signal	O—CH—O	1 proton
	δ=5.2—5.35 ppm	(m)	CH=CH	2 protons
	δ=7.3 ppm	(s)	C_6H_5	5 protons

4. 1 - (5 - carboxypentyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - (E) - 1 - octenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - (*E*) - 1 - octenyl] - 2 - pyrrolidone and 5 - bromopentanecarboxylic acid.

Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=4.35 ppm broad	signal	O—CH—O	1 proton
	δ=5.3—5.45 ppm	(m)	CH=H	2 protons

5. 1 - (7 - carboxyheptyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - (E) - 1 - octenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - (*E*) - 1 - octenyl] - 2 - pyrrolidone and 7 - bromoheptanecarboxylic acid.

Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=4.40 ppm broad singlet		O—CH—O	1 proton
	δ=5.25—5.40 ppm	(m)	CH=CH	2 protons

6. 1 - (6 - methoxycarbonylhexyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - 5 - ethoxy - (E) - pentenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - 4,4 - dimethyl - 5 - ethoxy - (*E*) - 1 - pentenyl] - 2 - pyrrolidone and 6 - bromohexanecarboxylic acid methyl ester.

Chromatography: toluene/ethyl acetate/methanol 5:4:0.3

NMR	δ=0.9 ppm	(s)	$C(CH_3)_3$	6 protons
	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons
IR	1680 cm^{-1}	νC=0		
	1730 cm^{-1}	νC=0		

7. 1 - (6 - methoxycarbonylhexyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3,4,4 - trimethyl - 5 - ethoxy - (E) - 1 - pentenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy)3,4,4 - trimethyl - 5 - ethoxy - (*E*) - 1 - pentenyl] - 2 - pyrrolidone and 6 - bromohexanecarboxylic acid methyl ester.

Chromatography: toluene/ethyl acetate/methanol 5:4:0.3

NMR	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
	δ=0.95 ppm	(s)	$C(CH_3)_3$	6 protons
	δ=4.45 ppm broad	signal	—O—OH—O—	1 proton
IR	1680 cm^{-1}	νC=0		
	1735 cm^{-1}	νC=0		

8. 1 - (6 - carboxyhexyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyl - (E) - 1 - octenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone and 6 - bromohexanecarboxylic acid.

Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=1.95 ppm	(s)	CH_3	3 protons
	δ=5.2—5.45 ppm	(m)	CH=CH	2 protons

9. 1 - (6 - carboxyhexyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - allyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone

From 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - allyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone and 6 - bromohexanecarboxylic acid.

Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.2—6.0 ppm	(m)	CH=CH, $CH=CH_2$	5 protons
	δ=4.45 ppm	(s, broad)	O—CH—O	1 proton

b) (I)

The compounds indicated under 1 to 9 are, unless otherwise stated, produced by splitting off the THP protective group from the compounds indicated in Example 4 a under 1 to 9 analogously to the instructions given in Example 3 n.

1. 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxy - (E) - 1 - decenyl) - 2 - pyrrolidone

Chromatography: ethyl acetate/toluene/glacial acetic acid 4:5:0.02

R_f=0.3

NMR	δ=5.1—5.4 ppm	(m)	CH=CH	2 protons

2. 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxy - 4,4 - dimethyl - (E) - 1 - octenyl) - 2 - pyrrolidone

Chromatography: ethyl acetate/glacial acetic acid. 98:2

NMR	δ=1.0 ppm	(s)	$C(CH_3)_2$	6 protons
	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons

3. 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxy - 5 - phenyl - (E) - 1 - pentenyl) - 2 - pyrrolidone

Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.2—5.35 ppm	(m)	CH=CH	2 protons
	δ=7.3 ppm	(s)	C_6H_5	5 protons

4. 1 - (5 - carboxypentyl) - 5 - (3 - hydroxy - (E) - 1 - octenyl) - 2 - pyrrolidone

Chromatography: ethyl acetate/glacial acetic acid 98:2

R_f=0.35

NMR	δ=5.3—5.45 ppm	(m)	CH=CH	2 protons

5. 1 - (7 - carboxyheptyl) - 5 - (3 - hydroxy - (E) - 1 - octenyl) - 2 - pyrrolidone

Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.25—5.40 ppm	(m)	CH=CH	2 protons
IR	1680 cm^{-1} —1705cm^{-1}	unresolved absorption of two νC=0		

6. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - pentenyl) - 2 - pyrrolidone

As a departure from the instructions given in Example 3 n, a 1% w/v solution of oxalic acid in methanol is used as the solvent instead of aqueous/ethanolic oxalic acid.

Chromatography: toluene/ethyl acetate/methanol 5:4:0.3

NMR	δ=0.9 ppm	(s)	$C(CH_3)_3$	6 protons
	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
	δ=5.2—5.4 ppm	(m)	CH=CH	2 protons
IR	1680 cm^{-1}	νC=0		
	1735 cm^{-1}	νC=0		

7. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 3,4,4 - trimethyl - 5 - ethoxy - (E) - 1 - pentenyl) - 2 - pyrrolidone

Splitting off the ether protective group as described above.

Chromatography: toluene/ethyl acetate/methanol 5:4:0.3

NMR	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
	δ=0.95 ppm	(s)	$C(CH_3)_3$	6 protons
IR	1685 cm^{-1}	νC=0		
	1735 cm^{-1}	νC=0		

8. 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxy - 3 - methyl - (E) - 1 - octenyl) - 2 - pyrrolidone
Chromatography: ethyl acetate/glacial acetic acid. 98:2

R_f=0.35

NMR	δ=1.95 ppm	(S)	CH_3	3 protons
	δ=5.25—5.40 ppm	(m)	CH=CH	2 protons

9. 1 - (6 - carboxyhexyl) - 5 - [3 - hydroxy - 3 - allyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone
Chromatography: ethyl acetate/glacial acetic acid 98:2

NMR	δ=5.2—6.0 ppm	(m)	CH=CH, $CH=CH_2$	5 protons
IR	1680—1705 cm^{-1}	broad absorption two unresolved νC=0		

c) (I)
1. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 3 - methyloctyl) - 2 - pyrrolidone
Analogous to Example 1, no. 1 by hydrogenation of 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxy - 3 - methyl - (*E*) - 1 - octenyl) - 2 - pyrrolidone and subsequent esterification with diazomethane. Physical data and chromatographic conditions of Example 1, No. 16.
2. 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxydecyl) - 2 - pyrrolidone
Analogous to Example 1 by hydrogenation of 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxy - (*E*) - 1 - decenyl) - 2 - pyrrolidone
Chromatography: ethyl acetate/toluene 5:5:0.02

R_f=0.33

d) (VI)
1 - (6 - methoxycarbonylhexyl) - 5 - (3 - oxo - 4,4 - dimethyl - 5 - ethoxy - (E) - 1 - pentenyl) - 2 - pyrrolidone
From 5 - (3 - oxo - (E) - 1 - pentenyl) - 4,4 - dimethyl - 5 - ethoxy - (*E*) - 1 - pentenyl) - 2 - pyrrolidone and 6 - bromohexanecarboxylic acid methyl ester analogously to Example 2 b.
Chromatography: toluene/ethyl acetate/methanol 5:4:0.3

NMR	δ=0.9 ppm	(s)	$C(CH_3)_3$	6 protons
	δ=3.7 ppm	(s)	$COOCH_3$	3 protons
	δ=5.5—6.2 ppm	(m)	CH=CH	2 protons
IR	1680 cm^{-1}	νC=0		

e) (I)

1. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 4,4 - dimethyl - 5 - ethoxy - (E) - I - pentenyl) - 2 - pyrrolidone
By reduction of the compound described under d) with zinc borohydride analogous to Example 3 e 1. For physical-chemical data see Example 4 b 6.
2. 1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 3,4,4 - trimethyl - 5 - ethoxy - (*E*) - 1 - pentenyl) - 2 - pyrrolidone
By reaction of the compound mentioned under 4 d) with methyl-magnesium iodide analogous to Example 2 c.
Physical-chemical data of Example 4 b 7.

f) (VII)
1 - (6 - carboxyhexyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 - methyloctyl] - 2 - pyrrolidone
From 1 - (6 - carboxyhexyl) - 5 - [3 - (tetrahydropyran - 2 - yloxy) - 3 -

methyl - (*E*) - 1 - octenyl] - 2 - pyrrolidone by hydrogenation analogous to Example 1, No. 1.
Chromatography; toluene/ethyl acetate/methanol 5:4:0.1

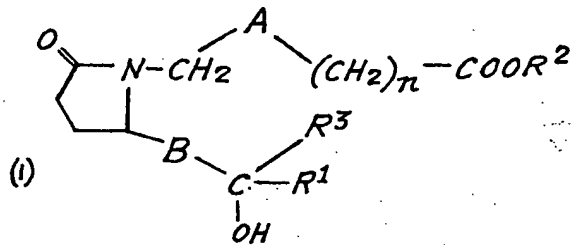
NMR δ=4.4 ppm (s, spread) O—CH—O

g) (I)
1 - (6 - methoxycarbonylhexyl) - 5 - (3 - hydroxy - 3 - methyloctyl) - 2 - pyrrolidone

From the compound described under 4 f) by splitting off the THP protective group and simultaneously esterifying the carboxy group analogously to Example 4 b 6 except that *p*-toluene-sulphonic acid is used as the catalyst instead of oxalic acid. Physical-chemical data of Example 1, No. 16.

WHAT WE CLAIM IS:—

1. A compound of the general formula I



(I)

in which

R^1 represents a straight or branched chain, saturated or unsaturated, aliphatic hydrocarbonyl radical having up to 10 carbon atoms or a cycloaliphatic hydrocarbyl radical having 3—7 carbon atoms, which radicals can each be substituted by

a) a straight chain alkoxy, alkylthio, alkenyloxy or alkenylthio radical having up to 5 carbon atoms,

b) a phenoxy radical which may itself be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from alkyl groups having 1—3 carbon atoms, halogen atoms, phenoxy radicals, and alkoxy radicals having 1—4 carbon atoms, which alkyl and phenoxy groups may be substituted by one or more halogen atoms,

c) a furyloxy, thienyloxy or benzyloxy radical each of which may be monosubstituted or disubstituted in the ring by one or two substituents selected, independently in the latter case, from halogen atoms, alkyl groups having 1—3 carbon atoms which may be substituted by one or more halogen atoms, and alkoxy groups having 1 to 4 carbon atoms,

d) a trifluoromethyl group or a pentafluoroethyl group,

e) a cycloalkyl radical having 3—7 carbon atoms,

f) a phenyl, thienyl, or furyl radical each of which may be monosubstituted or disubstitued by one or two substituents selected, independently in the latter case, from halogen atoms, alkyl groups having 1—3 carbon atoms which may be substituted by one or more halogen atoms, and alkoxy groups having 1—4 carbon atoms,

R^2 represents a straight or branched chain, saturated or unsaturated, aliphatic or cycloaliphatic hydrocarbon radical having 2—6 carbon atoms, an araliphatic hydrocarbon radical having 7 or 8 carbon atoms or, if R^1, R^3, A, B and *n* do not simultaneously represent a hydrogen atom, an *n*-pentyl group, a $—CH_2—CH_2—$ group, a —CH=CH— group and the integer three respectively, a methyl group or a hydrogen atom,

R^3 represents a hydrogen atom or a straight or branched chain alkyl, alkenyl, or alkynyl radical having up to 5 carbon atoms or an araliphatic hydrocarbon radical having 7 or 8 carbon atoms, A and B each represents a $—CH_2—CH_2—$ or a —CH=CH— group, wherein A and B may be the same or different but may not simultaneously be a —CH=CH— group,

n represents the integer two, three or four.

2. A compound as claimed in claim 1, wherein

R^1 represents a straight or branched chain, saturated or unsaturated, aliphatic

hydrocarbon radical having up to 7 carbon atoms or a cycloaliphatic hydrocarbon radical having 5 to 7 carbon atoms, which radicals can each be substituted by

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio radical having up to 4 carbon atoms

b) a phenoxy radical which may itself be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from alkyl groups having 1—3 carbon atoms, methoxy and ethoxy groups, trifluoromethyl groups, halogen atoms, and phenoxy radicals which may be substituted by one or more halogen atoms,

c) a thienyloxy or benzyloxy radical, each of which may be monosubstituted or disubstituted in the ring by one or two substituents selected, independently in the latter case, from alkyl groups having 1—3 carbon atoms, trifluoromethyl groups, halogen atoms, methoxy and ethoxy groups.

d) a trifluoromethyl group,

e) a cycloalkyl radical having 5—7 carbon atoms,

f) a phenyl radical or thienyl radical each of which may be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from alkyl groups having 1—3 carbon atoms, trifluoromethyl groups, halogen atoms, methoxy and ethoxy groups.

R^2 represents a straight or branched chain alkyl radical having 1—6 carbon atoms, a straight or branched chain alkenyl radical having 2—4 carbon atoms, a cycloalkyl radical having 5 or 6 carbon atoms or an aralkyl radical having 7 or 8 carbon atoms,

R^3 represents a hydrogen atom, a straight or branched chain alkyl radical having 1 to 5 carbon atoms, an alkenyl radical or alkynyl radical having 2 to 5 carbon atoms.

3. A compound as claimed in Claim 2, wherein

R^1 represents a straight or branched chain alkyl radical having 1—7 carbon atoms, a straight or branched chain alkenyl radical having 3—5 carbon atoms or a cycloalkyl radical having 5—7 carbon atoms, which radicals may be substituted by:

a) a straight or branched chain alkoxy, alkylthio, alkenyloxy or alkenylthio radical having up to 3 carbon atoms,

b) a phenoxy radical which may itself be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms, and phenoxy radicals optionally substituted by chlorine and/or fluorine atoms,

c) a thienyloxy or benzyloxy radical each of which may be monosubstituted or disubstituted in the nucleus by one or two substituents selected, independently in the latter case, from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms,

d) a trifluoromethyl group,

e) a cycloalkyl radical having 5—7 carbon atoms,

f) a phenyl radical or thienyl radical each of which may be monosubstituted or disubstituted by one or two substituents selected, independently in the latter case, from methyl, trifluoromethyl and methoxy groups, chlorine and fluorine atoms,

R^2 represents a straight-chain alkyl radical having 1 to 6 carbon atoms, a branched chain alkyl radical having 3—5 carbon atoms, a straight chain alkenyl radical having 2—4 carbon atoms, a cyclopentyl or cyclohexyl radical or a benzyl radical,

R^3 represents a hydrogen atom, a methyl, ethyl or propyl radical or an alkenyl or alkynyl radical having 2 or 3 carbon atoms, and

n represents the integer 3.

4. A compound as claimed in Claim 1 and which is named in Table I herein.

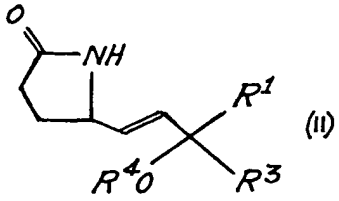
5. A compound as claimed in Claim 1 and which is described in any one of the Examples herein.

6. A salt of a free acid as claimed in any one of Claims 1 to 5.

7. A physiologically tolerable salt of a free acid as claimed in any one of Claims 1 to 5.

8. A process for the production of a compound of the general formula I, as claimed in Claim 1, wherein

a_1) a compound of formula II

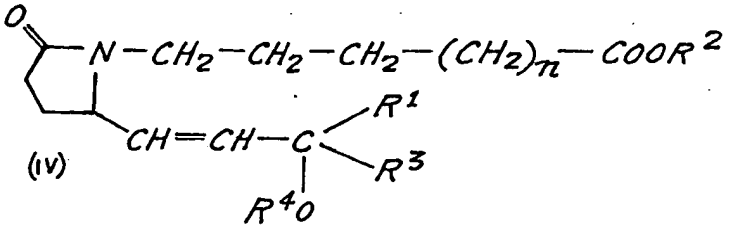


(II)

wherein R^1 and R^3 have the meanings given in Claim 1 and R^4 represents a protective group that can be split off under acidic conditions, is deprotonated at the nitrogen atom with a base and the anion thus formed is reacted with a carboxylic derivative of formula III

$$Y—CH_2—CH_2—CH_2—(CH_2)_n—COOR^2 \qquad III$$

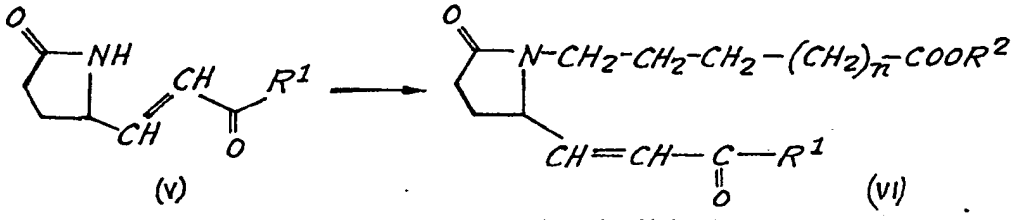
wherein R^2 and n have the meanings given in Claim 1 and Y represents a halogen atom, an alkanesulphonyloxy radical or a benzene sulphonyloxy radical that may be substituted by one or more substituents selected from alkyl groups and halogen atoms, to form a compound of formula IV



(IV)

a_2) the hydroxy protective group R^4 is split off from the compound of formula IV by acid hydrolysis to form a compound of formula I in which A represents a $—CH_2—CH_2—$ group and B represents a —CH=CH— group, or

$a_{2.1}$) a compound of formula V is reacted as described under a_1) to form a compound of formula VI



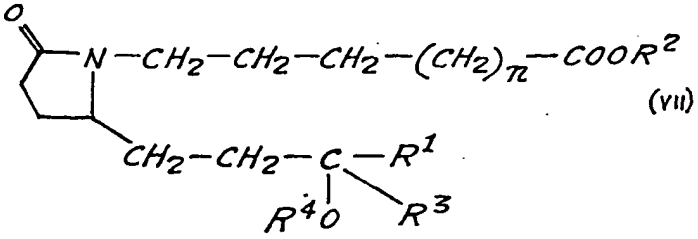
(V) (VI)

wherein R^1, R^2 and n have the meanings given in Claim 1,

$a_{2.2}$) the exocyclic carbonyl group in the compound of formula VI is reduced or the compound of formula VI is reacted with an organometallic compound produced from $R^3—X^{\sim}$, wherein $X^{\sim}$ represents a halogen atom, R_3 has the meaning given in Claim 1 but cannot be hydrogen, to form a compound of formula I wherein A represents a $—CH_2—CH_2—$ group and B represents a —CH=CH— group, and optionally

a_3) a compound of formula I in which A represents a $—CH_2—CH_2—$ group and B represents a —CH=CH— group, is hydrogenated to give a compound of formula I wherein A and B each represents a $—CH_2—CH_2—$ group, or

$a_{3.1}$) a compound of formula IV is hydrogenated to form a compound of formula VII-

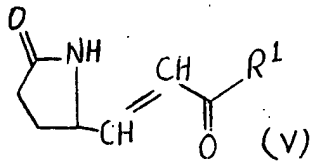


(VII)

wherein R^1, R^2, R^3 and n have the meanings given in Claim 1 and R^4 is as defined above and

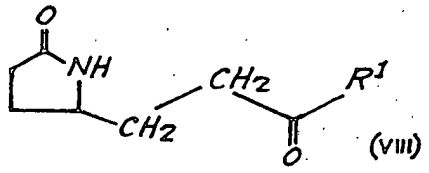
$a_{3.2}$) the hydroxy protective group in the compound of formula VII is split off by acid hydrolysis to form a compound of formula I wherein A and B each represents a $-CH_2-CH_2-$ group, or

$b_{1.1}$) in a compound of formula V



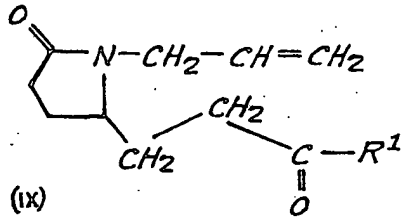
(V)

the double bond is hydrogenated to give a compound of formula VIII wherein R^1 has the meaning given in Claim 1



(VIII)

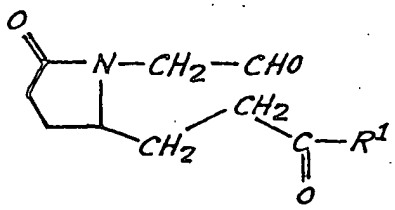
$b_{1.2}$) the compound of formula VIII is deprotonated at the nitrogen with a base and the anion formed is reacted with an allyl halide to form a compound of formula IX



(IX)

wherein R^1 has the meaning given in Claim 1,

$b_{1.3}$) the compound of formula IX is subjected to ozonolysis whereby an aldehyde of formula X is formed



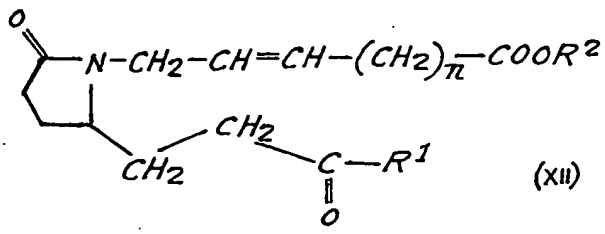
(X)

wherein R^1 has the meaning given in Claim 1,

$b_{1.4}$) the aldehyde of formula X is reacted with an ylide of formula XI

$$(R^5)_3P=CH(CH_2)_nCOOR^2 \qquad \text{XI}$$

wherein n and R^2 have the meanings given in Claim 1 and R^2 may also represent an alkali metal cation, the symbols R^5 each represents the same or different straight chain (C_1—C_4)-alkyl radical or phenyl radical, to form a compound of formula XII

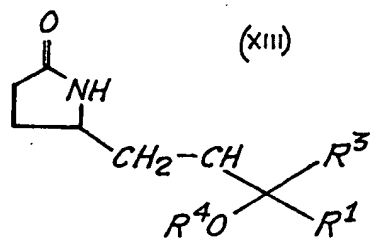


(XII)

wherein R^1, R^2 and n have the meanings given in Claim 1,

$b_{1.5}$) the exocyclic carbonyl group of the compound of formula XII is reacted with an organometallic compound produced from R^3—X~, wherein X~ represents a halogen atom and R^3 has the meaning given for formula I but may not be hydrogen, or the exocyclic carbonyl group in the compound of formula XII is reduced to form a compound of formula I wherein A represents a —CH=CH— group and B represents a $—CH_2—CH_2—$ group, or

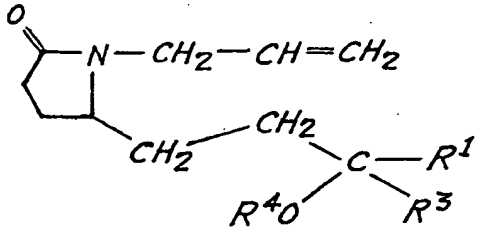
$b_{2.1}$) the double bond in a compound of formula II is hydrogenated to form a compound of formula XIII



(XIII)

wherein R^1 and R^3 have the meanings given in Claim 1, and R^4 is as defined above,

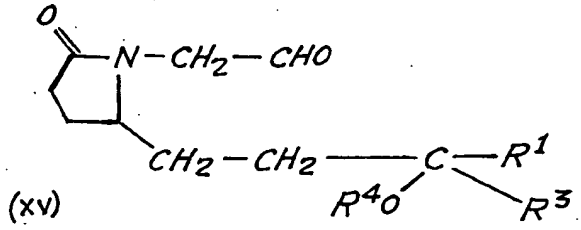
$b_{2.2}$) the compound of formula XIII is deprotonated at the nitrogen with a base and the anion formed is reacted with an allyl halide to form a compound of formula XIV



(XIV)

wherein R^1 and R^3 have the meanings given in Claim 1, and R^4 is as defined above,

$b_{2.3}$) the compound of formula XIV is subjected to ozonolysis whereby an aldehyde of formula XV is formed



(XV)

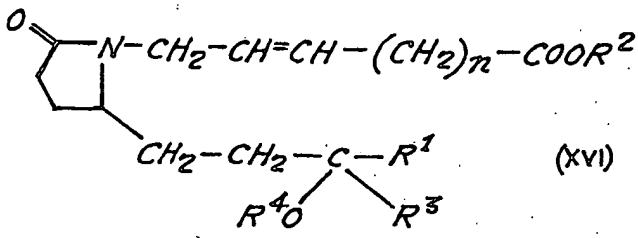
wherein R^1 and R^3 have the meanings given for formula I and R^4 is as defined above,

$b_{2.4}$) the aldehyde of formula XV is reacted with an ylide of formula XI

$$(R^5)_3P=CH(CH_2)_nCOOR^2 \qquad \text{XI}$$

wherein n and R^2 have the meanings given in Claim 1 and R^2 may also represent an

alkali metal cation and the symbols R^5 are as defined above, to form a compound of formula XVI



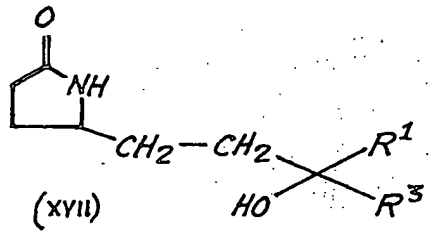
(XVI)

wherein R^1, R^2, R^3 and n have the meanings given for formula I and R^4 is as defined above,

$b_{2.5}$) the protective group R^4 is split off from the compound of formula XVI by acid hydrolysis to form a compound of formula I wherein A represents a —CH=CH— group and B represents a $—CH_2—CH_2—$ group, and optionally

b_3) a compound of formula I, wherein A represents a —CH=CH— group and B represents a $—CH_2—CH_2—$ group, is hydrogenated to form a compound of formula I wherein A and B each represent a $—CH_2—CH_2—$ group, or

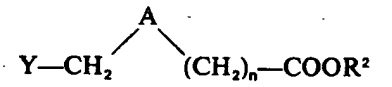
$b_{4.1}$) the exocyclic carbonyl group in the compound of formula VIII is reduced, or the compound of formula VIII is reacted with an organo-metallic compound produced from $R^3—X^{\sim}$, wherein $X^{\sim}$ represents a halogen atom and R^3 has the meaning given in Claim 1 but cannot represent hydrogen, to form a compound of formula XVII



(XVII)

wherein R^1 and R^3 have the meanings given in Claim 1 and

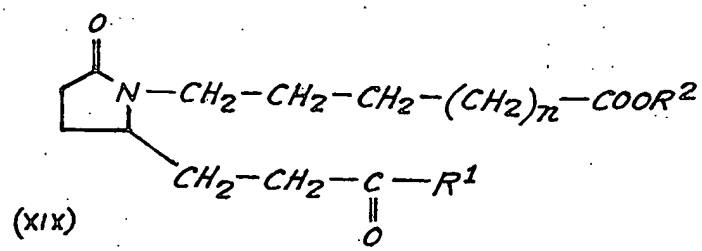
$b_{4.2}$) the compound of formula XVII is deprotonated at the nitrogen with a base and the anion formed is reacted with a carboxylic acid derivative of formula XVIII



XVIII

wherein R^2, A and n have the meanings given in Claim 1 and Y is as defined above to form a compound of formula I wherein A represents a $—CH_2—CH_2—$, or a —CH=CH— group and B represents a $—CH_2—CH_2—$ group, or

c_1) a compound of formula VIII is deprotonated at the nitrogen with a base and the anion formed is reacted with a carboxylic acid derivative of formula III to form a compound of formula XIX



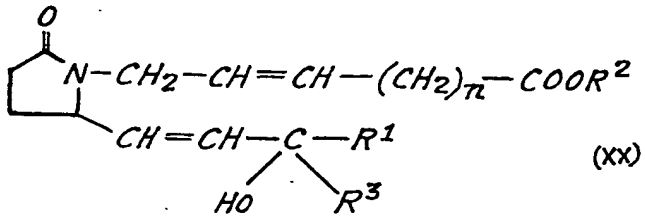
(XIX)

wherein R^1, R^2 and n have the meanings given in Claim 1 and

c_2) the exocyclic carbonyl group of the compound of formula XIX is reduced or the compound of formula XIX is reacted with an organometallic compound produced from $R^3—X^{\sim}$, wherein $X^{\sim}$ represents a halogen atom and R^3 has the meaning mentioned in Claim 1 but cannot represent hydrogen, to form a

compound of formula I wherein A and B each represent a $-CH_2-CH_2-$ group, or

d) a compound of formula XX



(XX)

is hydrogenated, whereby a compound of formula I is formed, wherein A and B each represent a $-CH_2-CH_2-$ group, or

e) any one or more of the steps defined above is carried out analogously using a reactant analogous to a compound as defined above but in which a free hydroxyl group is present instead of a group OR^4, or a group OR^4 is present instead of a free hydroxyl group, as appropriate, R^4 being as defined above, and

f) if desired, a compound of formula I resulting from any of the above reactions is converted into a salt thereof.

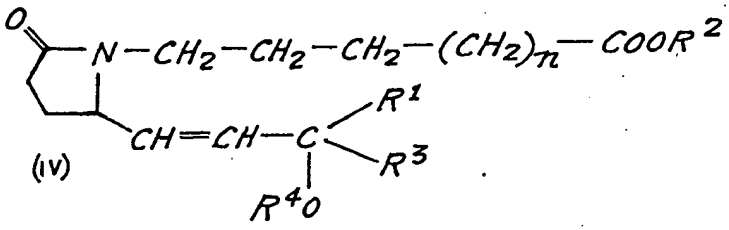
9. A process as claimed in Claim 8, carried out substantially as described in any one of the Examples herein.

10. A compound as claimed in Claim 1, whenever produced by a process as claimed in Claim 8 or Claim 9.

11. A pharmaceutical preparation which comprises a compound as claimed in any one of Claims 1 to 5 or Claim 10, or a physiologically tolerable salt thereof as active substance, in admixture or conjunction with a pharmaceutically suitable carrier.

12. A pharmaceutical preparation as claimed in Claim 11, which also comprises one or more further active substances.

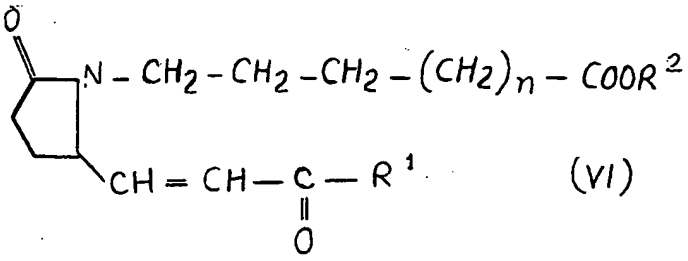
13. Compounds of formula IV



(IV)

wherein R^1, R^2 and R^3 are as defined in Claim 1, and R^4 is as defined in Claim 8.

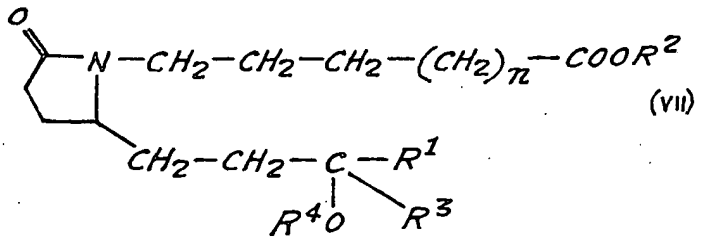
14. Compounds of formula VI



(VI)

wherein R^1 and R^2 are as defined in Claim 1.

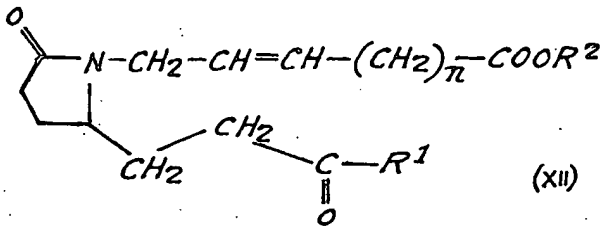
15. Compounds of formula VII



(VII)

wherein R^1, R^2 and R^3 are as defined in Claim 1 and R^4 is as defined in Claim 8.

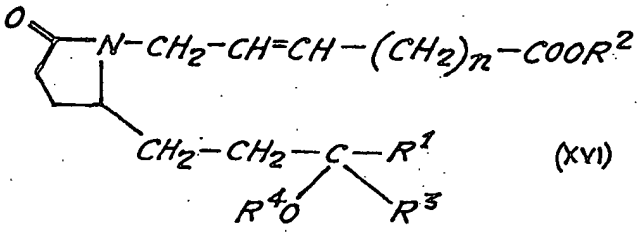
16. Compounds of formula XII



(XII)

wherein R^1 and R^2 are as defined in Claim 1.

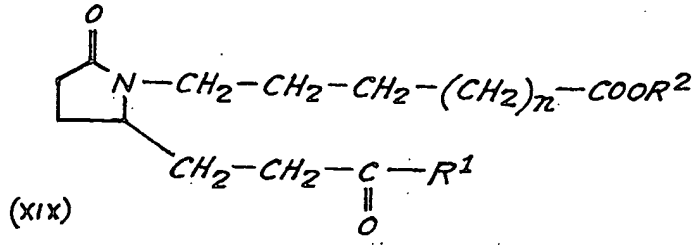
17. Compounds of formula XVI



(XVI)

wherein R^1 and R^3 are as defined in Claim 1 R^4 is as defined in Claim 8.

18. Compounds of formula XIX



(XIX)

wherein R^1 and R^2 are as defined in Claim 1.

ABEL & IMRAY,
Chartered Patent Agents,
Northumberland House,
303—306 High Holborn,
London, WC1V 7LH.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.